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Stem-cell Therapy for Peripheral Arterial Disease

Policy # 00298
Original Effective Date: 06/15/2011
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Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the treatment of peripheral arterial disease (PAD), including critical limb ischemia, with injection or infusion of cells concentrated from bone marrow aspirate to be **investigational.***

Background/Overview

Critical limb ischemia due to PAD results in pain at rest, ulcers, and significant risk for limb loss. Injection of hematopoietic stem cells concentrated from bone marrow is being evaluated for the treatment of critical limb ischemia when surgical or endovascular revascularization has failed.

Peripheral arterial disease is a common atherosclerotic syndrome that is associated with significant morbidity and mortality. A less-common cause of PAD is Buerger disease, also called thromboangitiis obliterans, which is a nonatherosclerotic 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. Critical limb ischemia (CLI) is the endstage 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. The standard therapy for severe, limb-threatening ischemia is revascularization aiming to improve blood flow to the affected extremity. If revascularization has failed or is not possible, amputation is often necessary.

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

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(diabetes, smoking, hyperlipidemia and advanced age) are also risk factors for a lower number of circulating progenitor cells.

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. The SmartPReP2®‡ Bone Marrow Aspirate Concentrate System (Harvest Technologies) has been developed as a single-step point-of-care, bedside centrifugation system for the concentration of stem cells from bone marrow. The system is composed of a portable centrifuge and an accessory pack that contains processing kits including a functionally closed dual-chamber sterile processing disposable. The SmartPReP2 system is designed to concentrate a buffy coat of 20 mL from whole bone marrow aspirate of 120 mL.

The concentrate of bone marrow aspirate contains a mix of cell types, including lymphocytoid cells, erythroblasts, monocytoid cells, and granulocytes. Following isolation and concentration, the hematopoietic stem-cell/bone marrow concentrate is administered either intra-arterially or through multiple injections (20 to 60) into the muscle, typically in the gastrocnemius. Other methods of concentrating stem cells include the in vitro expansion of bone marrow-derived stem cells or use of granulocyte colony-stimulating factor to mobilize peripheral blood mononuclear cells. There is some discrepancy in the literature regarding the nomenclature of cell types. Studies addressed in this policy include the use of mononuclear cells/monocytes and/or mesenchymal stem cells.

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 CLI include the Rutherford criteria for limb status, healing of ulcers, the ankle-brachial index (ABI), transcutaneous oxygen pressure (TcO2), and pain-free walking. The Rutherford criteria include ankle and toe pressure, the level of claudication, ischemic rest pain, tissue loss, nonhealing ulcer, and gangrene. 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). An increase greater than 0.1 is considered to be clinically significant. TcO2 is measured with an oxymonitor; the normal value is 70-90 mm Hg. Pain-free walking may be measured by time on a treadmill, or more frequently, by distance in a 400-meter walk.

FDA or Other Governmental Regulatory Approval

U.S. FDA
Two devices have been identified that provide point-of-care concentration of bone marrow aspirate:

- The SmartPReP2 Bone Marrow Aspirate Concentrate System is a microprocessor-controlled dedicated centrifuge with decanting capability and an accessory BMAC IDE PAD Pack for processing a patient's bone marrow aspirate. The system is in a Phase III trial; expected completion of the trial is in 2014.
- The MarrowStim P.A.D. kit™‡ (Biomet Biologics) is in a Phase III trial for the treatment of PAD with completion expected May 2014.

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Ixmyelocel-T (Aastrom) is an expanded stem cell product where bone marrow aspirate is sent to a processing facility to be cultured in a bioreactor and expanded over a 2-week period. The expanded cell population is enriched with mesenchymal precursors and alternatively-activated macrophages. This product is currently being evaluated in a pivotal Phase III trial regulated by the FDA's Center of Biologic Evaluation and Research.

Pluristem is developing allogeneic cell therapy derived from full-term placenta (PLX-PAD cells). This product has been tested in a Phase I trial in patients with critical limb ischemia.

Centers for Medicare and Medicaid Services (CMS)
There is no national coverage determination.

Rationale/Source

The most recent update was performed through April 8, 2013. At this time, the literature consists primarily of case series, small Phase II studies, and review articles. Systematic reviews, controlled studies, and the larger case series are described below.

A 2011 Cochrane review identified 2 small studies with a total of 57 patients that met the review's inclusion criteria for local intramuscular transplantation of autologous mononuclear cells (monocytes) for CLI. Studies were excluded that used mesenchymal stem cells (MSCs) or bone marrow aspirate. In one of the studies, intramuscular injection of bone marrow-derived mononuclear cells was compared with standard conservative treatment. In the second study, peripheral blood derived mononuclear cells were collected following injections of granulocyte colony-stimulating factor and transplanted by intramuscular injections. Both studies showed a significant reduction in amputations with treatment with monocytes, but larger randomized controlled trials are needed to adequately evaluate the effect of treatment with greater certainty.

In 2012, Liu et al. reported a meta-analysis of 6 randomized trials (333 patients) that evaluated mononuclear cell transplantation in patients with CLI. Cell therapy was found to decrease the incidence of amputation in patients with CLI with an odds ratio (OR) of 0.37. The rate of amputation free survival was increased in patients with Rutherford class 5 CLI (OR: 3.28) but was not significantly different in patients with Rutherford class 4. Following is a description of some of the randomized controlled trials (RCTs) that were included in the meta-analysis.

Concentrated Bone Marrow Aspirate (Monocytes and Mesenchymal Stem Cells)
Randomized Controlled Trials
Intramuscular Injection. Prochazka and colleagues reported a randomized study of 96 patients with critical limb ischemia and foot ulcer in 2010. Patient inclusion criteria were critical limb ischemia as defined by ankle-brachial index (ABI) equal to or less than 0.4, ankle systolic pressure equal to or less than 50 mm Hg or toe systolic pressure equal to or less than 30 mm Hg, and failure of basic conservative and revascularization treatment (surgical or endovascular). The patients were randomized into treatment with bone marrow concentrate (n=42) or standard medical care (n=54). The primary endpoints were major limb amputation during 120 days and degree of pain and function at 90- and 120-day follow-up. At baseline, the

control 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% - all respectively). In addition, the control group had a higher proportion of patients with stage DIII (deep ulcers with osteitis) University of Texas Wound Classification (72% vs. 40%, respectively). 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. Forty-two of the 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. The reason for different times of follow-up for the primary outcome measure is unclear. Five patients in the bone-marrow group and 8 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 performed only in the group treated with bone marrow concentrate. In the treatment group with salvaged limbs, toe pressure and toe brachial index increased from 22.66 to 25.63 mm Hg and from 0.14 to 0.17, respectively. Interpretation of this study is limited by unequal baseline measures, lack of blinding, different periods of follow-up, different loss to follow-up and different measures at follow-up for the 2 groups.

In 2011, Benoit et al. reported an FDA-regulated double-blind pilot RCT of 48 patients with CLI who were randomized in a 2:1 ratio to bone marrow concentrate using the SmartPReP system or iliac crest puncture with intramuscular injection of diluted peripheral blood. At 6-month follow-up, the difference in the percentage of amputations between the cell therapy group and controls (29.4% vs. 35.7%, respectively) did not achieve statistical significance. 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 than placebo (39.1% vs. 71.4%, respectively). Power analysis indicated that 210 patients would be needed to achieve 95% power in a planned pivotal trial.

Intra-arterial Injection. Results from the multi-center PROVASA trial (Intraarterial Progenitor Cell Transplantation of Bone Marrow Mononuclear Cells for Induction of Neovascularization in Patients with Peripheral Arterial Occlusive Disease) were reported in 2011. In this double-blind Phase II 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 bone marrow-derived mononuclear cells (BM-MNC) or placebo. The cell suspension included hematopoietic, mesenchymal, and other progenitor cells. After 3 months, both groups were treated with BM-MNC in an open-label phase. Twelve patients received additional treatment with BM-MNC between 6 and 18 months. The primary outcome measure, a significant increase in the ABI 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 the groups. There was a significant improvement in ulcer healing (ulcer area 1.89 cm2 vs. 2.89 cm2) and reduced pain at rest (improvement of about 3 vs. 0.05) following intra-arterial BM-MNC administration. This is the only randomized controlled trial to report intra-arterial administration of BM-MNC.

Observational Studies

A 2008 TACT report by Matoba et al. assessed the 3-year safety and clinical outcomes of intramuscular implantation of bone marrow-mononuclear cells in a series of 74 patients with critical limb ischemia due to atherosclerotic PAD and 41 patients with thromboangiitis obliterans (TAO; Buerger disease). The ischemic

limbs were not candidates for surgical or nonsurgical revascularization. Twenty-six patients (23%) had a previous bypass operation. Bone marrow cells were aspirated from the ileum and the mononuclear cells sorted and concentrated to a final volume of 40 mL. The cells were implanted by intramuscular injection into the foot. Patients were followed every week for 4 weeks and at 6, 12, 24, and 36 months thereafter. The overall survival, amputation-free interval, adverse events, ABI, TcO2, pain scale, ulcer size, and pain-free walking distance were evaluated at each time point. Three-year overall survival rates were 80% in patients with atherosclerotic PAD and 100% for patients with TAO, and the median follow-up time of surviving patients was 25 months (range, 0.8 to 69 months). The 3-year amputation-free rate was 60% in atherosclerotic PAD and 91% in patients with TAO. Of the 24 amputations in patients with PAD, 83% occurred within 6 months. The ABI and transcutaneous oxygen pressure value did not significantly change, but there was a significant improvement in the leg pain scale (from 6 to 2), ulcer size (from 3.5 cm2 to 0), and pain-free walking distance (from about 25 meters to 100 meters) at 6 months.

Amann et al. reported a pilot study of autologous bone marrow cell transplantation in 51 consecutive patients with impending major amputation due to end-stage CLI in 2009. Forty-five patients (88%) had undergone a mean of 2 unsuccessful attempts of operative and/or percutaneous revascularization of the ischemic limb. Six patients (12%) were technically not amenable to revascularization. Major amputation (above the ankle) had been recommended to 46 of the 51 patients (90%) by the treating vascular surgeons. For the first 12 subjects, 450-500 mL bone marrow was aspirated under general anesthesia and processed by the Ficoll method. For the remaining subjects, 240 mL bone marrow was aspirated under sedation and processed using an automated bedside density gradient centrifugation method. Patients were seen monthly up to 6 months and at least in half-year intervals after. Minimum follow-up was 6 months, and the mean follow-up was 411 days (range 175 to 1,186 days). No patients were lost to follow-up. Improvement in perfusion and subsequent limb salvage was achieved in 30/51 patients (59%) at 6 months and 27/51 (53%) at last follow-up (mean of 411 days). Seventeen minor amputations (6 forefoot and 11 toe) were performed in the 30 patients with 24-week limb salvage. Complete wound healing was achieved in 15 of 21 patients with ischemic wounds. Perfusion increased in patients with limb salvage and did not change in patients who eventually underwent major amputation. Patients with limb salvage improved from a mean Rutherford category of 4.9 at baseline to 3.3 at 6 months. Analgesic consumption was reduced by 62%. Total walking distance improved in non-amputees from a median of 0 to 40 meters at 24 weeks. No unexpected long-term adverse events occurred.

Adverse Events
In 2012, Johnsson et al. reported a high incidence of serious adverse events in patients treated with peripheral blood mononuclear cells, causing the investigators to terminate the study. Out of 9 patients, 2 had a myocardial infarction that was believed to be related to the bone marrow stimulation, and 1 of the 2 patients died. Another patient had a minor stroke 1 week after stem-cell implantation.

Expanded Monocytes and Mesenchymal Stem Cells
Randomized Controlled Trials
Interim and final results from the industry-sponsored Phase II randomized double-blind placebo-controlled RESTORE-CLI trial, which utilized cultured and expanded monocytes and MSCs derived from bone marrow aspirate (ixmyelocel-T), were reported by Powell et al. in 2011 and 2012. 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 difference in amputations at 12 months.

Comparative Studies

Randomized Controlled Trials

A 2011 study by Lu et al. was a randomized double-blind safety and feasibility study of 41 patients with bilateral diabetic CLI and foot ulcer who were injected intramuscularly with expanded bone marrow MSCs or bone marrow-derived monocytes in one limb and normal saline in the other limb. At 24 weeks after treatment, outcomes (painless walking time, ankle-brachial index, transcutaneous oxygen pressure, and magnetic resonance angiography) were significantly improved in both experimental groups compared to injection with normal saline. Outcomes on some outcome measures were modestly improved for treatment with MSCs compared to mononuclear cells. Ulcer healing at 24 weeks occurred in 100% of experimental limbs with a faster rate of healing in the MSC-treated limbs. No cell-treated limbs underwent amputation, compared to 6 of 37 control limbs.

In 2002, the Therapeutic Angiogenesis by Cell Transplantation (TACT) study investigators published results of a pilot study and a small double-masked trial with 22 patients who were treated with bone marrow-mononuclear cells by intramuscular injection into the gastrocnemius of one leg and peripheral blood-mononuclear cells in the other leg as a control (randomized order). Patients qualified for marrow implantation if they had bilateral chronic limb ischemia, including rest pain, non-healing ischemic ulcers, or both, and were not candidates for nonsurgical or surgical revascularization. Seventeen patients (85%) had been previously treated with percutaneous angioplasty, bypass graft, or both. The patients had resting ABI less than 0.6 in both limbs. Patients with poorly controlled diabetes mellitus or with evidence of malignant disorder during the past 5 years were excluded from the study. About 500 mL of bone marrow cells were aspirated from the ileum, separated, and concentrated to a final volume of about 30 mL. About 3 hours after marrow aspiration the cells were implanted by intramuscular injection into the gastrocnemius. Follow-up with ABI, transcutaneous oxygen pressure (TcO2) and pain-free walking time was performed every week for 4 weeks and every 4 months thereafter. Two patients discontinued the study after randomization due to clinical worsening before 4 weeks. At 4 weeks after treatment, ABI, TcO2, and rest pain were significantly improved in legs injected with bone marrow-mononuclear cells, compared with those injected with peripheral blood-mononuclear cells. For example, ABI increased by 0.1 in the leg treated with bone marrow-mononuclear cell and by 0.02 with peripheral blood-mononuclear cells. TcO2 improved by 17.4 mm Hg with bone marrow-mononuclear cells and by 4.6 mm Hg with peripheral blood-mononuclear cells. Rest pain in legs treated with bone marrow-mononuclear cells was resolved in 16 of 20 patients, while pain in legs treated with peripheral blood-mononuclear cells remained in 17 of 20 patients. These improvements were sustained at 24 week follow-up. Digital subtraction angiography showed a marked increase in the number of visible collateral vessels in 60% of legs treated with bone marrow cells. No adverse events were reported.

Ongoing Clinical Trials

A 2012 update on clinical trials evaluating the effect of biologic therapy in patients with CLI describes several products that are currently in Phase II or Phase III trials. The U.S. FDA recommends that the primary efficacy endpoint in a Phase III CLI trial should be amputation-free survival. When the probability of

this outcome is combined with the comorbid burden of CLI patients and variable natural history, large numbers of patients (about 500) may be needed to evaluate clinical outcomes.

The design of the BONe Marrow Outcome Trial in Critical Limb Ischaemia (BONMOT-CLI) trial was reported in 2008. It is an investigator-initiated, randomized, double-blinded, placebo-controlled multicenter study at 4 sites in Germany that assesses the therapeutic value of bone marrow cell-induced angiogenesis and arteriogenesis in severe, limb-threatening ischemia. Ninety patients with no option for revascularization or after failed revascularization will be randomized to 40 injections into the ischemic limb with a concentrate of autologous bone marrow cells or to sham bone marrow aspiration and 40 placebo injections. The combined primary endpoint is major amputation or persisting critical limb ischemia (no improvement) over 3 months. Secondary endpoints are death, changes in perfusion, quality of life, walking distance, minor amputations, wound healing, collateral density and cancer incidence. Post study follow-up is 2 years.

JUVENTAS (Rejuvenating Endothelial Progenitor Cells via Transcutaneous Intra-arterial Supplementation) is a randomized, double-blind, placebo-controlled trial in the Netherlands. The clinical effects of repeated intra-arterial infusion of bone marrow mononuclear cells will be investigated in 110-160 patients with critical limb ischemia. Patients will receive repeated intra-arterial infusion of bone marrow-mononuclear cells or placebo into the common femoral artery. The primary outcome measure is the rate of major amputation after 6 months. Secondary endpoints include minor amputation, number and extent of leg ulcers, resolution of rest pain, perfusion, change in quality of life, and change in clinical status. Functional characteristics of the bone marrow-mononuclear cells will also be studied, and the bone marrow-mononuclear cell dysfunction will be related to clinical outcome.

A search of online site ClinicalTrials.gov in April 2013 and a 2012 review by Powell, identified a number of ongoing trials with concentrated or expanded stem cells for peripheral arterial disease, including:

- A manufacturer-sponsored U.S. multicenter Phase III study on the use of autologous bone marrow cells for the treatment of critical limb ischemia due to PAD. Completion of this study of ixmyelocel-T (REVIVE) is expected mid-2015 (NCT01483898).
- A manufacturer-sponsored Phase III trial with bone marrow aspirate concentrate with the SmartPReP2 system for the treatment of critical limb ischemia (NCT01245335). This is a U.S. pivotal randomized double-blind safety and efficacy trial comparing bone marrow aspirate concentrate with placebo injection into ischemic tissue of the lower extremity in 210 patients. The study start date is listed as January 2011; the expected study completion date is June 2014.
- A manufacturer-sponsored sham-controlled Phase III trial of Biomet Biologic's MarrowStim P.A.D. kit (NCT01049919) is currently recruiting. The study has an estimated enrollment of 152 patients with completion expected May 2014.
- A Phase I study of placenta-derived mesenchymal-like stromal cells (PLX-PAD) by Pluristem has been completed (NCT00951210) A Phase II study in patients with CLI is expected to begin in 2013. A Phase II study of PLX-PAD for the treatment of intermittent claudication (NCT01679990) is currently recruiting with a target enrollment of 150 patients and completion in December 2015.

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Summary
Based on initial evidence from case series and small randomized trials, injection of bone marrow concentrate may hold promise as a treatment for critical limb ischemia due to peripheral arterial disease. The current literature consists primarily of case series and Phase II studies using a variety of cell preparation methods. Well-designed and well-conducted randomized controlled trials with a larger number of subjects are needed to evaluate the health outcomes of these procedures. A number of trials are in progress, including several large randomized double-blind placebo controlled trials. Results from these trials are needed to adequately evaluate the impact on net health outcome of these procedures. Further information on the safety and durability of the treatment is also needed. Therefore, infusion or injection of stem cells for peripheral arterial disease is considered investigational.

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	0263T, 0264T, 0265T
HCPCS	No codes
ICD-9 Diagnosis	All relative diagnoses
ICD-9 Procedure	99.79

Policy History

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06/02/2011 Medical Policy Committee review
06/15/2011 Medical Policy Implementation Committee approval. New policy.
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06/18/2014 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
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*****Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

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A. whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. FDA and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
    2. credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
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