PROLOTHERAPY FOR MUSCULOSKELETAL INDICATIONS

Policy Number: 2017T0498L  Effective Date: May 1, 2017

INSTRUCTIONS FOR USE
This Medical Policy provides assistance in interpreting UnitedHealthcare benefit plans. When deciding coverage, the member specific benefit plan document must be referenced. The terms of the member specific benefit plan document [e.g., Certificate of Coverage (COC), Schedule of Benefits (SOB), and/or Summary Plan Description (SPD)] may differ greatly from the standard benefit plan upon which this Medical Policy is based. In the event of a conflict, the member specific benefit plan document supersedes this Medical Policy. All reviewers must first identify member eligibility, any federal or state regulatory requirements, and the member specific benefit plan coverage prior to use of this Medical Policy. Other Policies and Coverage Determination Guidelines may apply. UnitedHealthcare reserves the right, in its sole discretion, to modify its Policies and Guidelines as necessary. This Medical Policy is provided for informational purposes. It does not constitute medical advice.

UnitedHealthcare may also use tools developed by third parties, such as the MCG™ Care Guidelines, to assist us in administering health benefits. The MCG™ Care Guidelines are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

BENEFIT CONSIDERATIONS
Before using this policy, please check the member specific benefit plan document and any federal or state mandates, if applicable.

Essential Health Benefits for Individual and Small Group
For plan years beginning on or after January 1, 2014, the Affordable Care Act of 2010 (ACA) requires fully insured non-grandfathered individual and small group plans (inside and outside of Exchanges) to provide coverage for ten categories of Essential Health Benefits ("EHBs"). Large group plans (both self-funded and fully insured), and small group ASO plans, are not subject to the requirement to offer coverage for EHBs. However, if such plans choose to provide coverage for benefits which are deemed EHBs, the ACA requires all dollar limits on those benefits to be removed on all Grandfathered and Non-Grandfathered plans. The determination of which benefits constitute EHBs is made on a state by state basis. As such, when using this policy, it is important to refer to the member specific benefit plan document to determine benefit coverage.

COVERAGE RATIONALE
Prolotherapy is unproven and not medically necessary.
The available studies are limited to those that include short to medium term follow-up with no significant functional improvement compared to placebo. Additional studies are needed to further define treatment parameters and to determine whether a clinically significant improvement is achieved.
APPLICABLE CODES

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Coverage Determination Guidelines may apply.

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<tr>
<th>CPT Code</th>
<th>Description</th>
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<tr>
<td>0232T</td>
<td>Injection(s), platelet rich plasma, any site, including image guidance, harvesting and preparation when performed</td>
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<table>
<thead>
<tr>
<th>HCPCS Code</th>
<th>Description</th>
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<td>M0076</td>
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DESCRIPTION OF SERVICES

Prolotherapy (also referred to as intra-articular regeneration injection therapy, proliferant therapy or proliferation therapy) has been claimed to promote healing by injecting a solution into the joints or ligaments that stimulates an inflammatory reaction. These solutions may include dextrose, glucose, glycerin, dextrose-gllycerine-phenol solution, zinc sulfate, fibrin glue, platelet-rich plasma or sodium morrhuate.

CLINICAL EVIDENCE

Low Back Pain

The evidence from published studies indicates that prolotherapy may provide very limited, short-term benefits for chronic back pain (CLBP). While prolotherapy improved CLBP in the short-term, the benefit was not maintained for more than a few weeks and outcomes were similar for placebo and treatment groups at 5-24 months. Prolotherapy may involve a single injection or a series of injections, often diluted with a local anesthetic.

A systematic review by Chou et al. (2009) included 174 articles of which 97 met criteria to assess the benefits and harms of nonsurgical interventional therapies for low back and radicular pain. Of the 97, only 5 addressed prolotherapy. Three of these studies found no difference between prolotherapy and either saline or local anesthetic control injections for short- or long-term (up to 24 months) pain or disability. One higher quality trial found prolotherapy associated with increased likelihood of short-term improvement in pain or disability versus control injection, but both treatment groups received a number of co-interventions including spinal manipulation, local injections, exercises, and walking. In the fifth trial, effects of prolotherapy could not be determined because the prolotherapy group received strong manipulation and the control injection group only light manipulation. The authors concluded that prolotherapy has not been found to be effective for the treatment of low back and radicular pain.

A systematic review by Dagenais et al. (2008) of articles on prolotherapy published from 1997 to 2007 concluded that prolotherapy is one of a number of treatments recommended for CLBP. Prolotherapy has a long history of use, a reasonable but not proven theoretical basis, a low complication rate, and conflicting evidence of efficacy.

In a 2007 Cochrane Review on prolotherapy injections for CLBP, Dagenais et al. concluded that there is conflicting evidence regarding the efficacy of prolotherapy injections for patients with chronic low-back pain. When used alone, prolotherapy is not an effective treatment for chronic low-back pain. When combined with spinal manipulation, exercise, and other co-interventions, prolotherapy may improve chronic low-back pain and disability. Conclusions are confounded by clinical heterogeneity amongst studies and by the presence of co-interventions.

Prolotherapy is considered to be contraindicated in patients with metastatic cancer, non-musculoskeletal pain, spinal anatomical defects, systemic inflammation, morbid obesity, bleeding disorders, low pain threshold, inability to perform post treatment exercises, chemical dependency, or whole body pain. Because high doses of a prolotherapy solution containing dextrose 12.5%, glycerin 12.5%, phenol 1.0%, and lidocaine 0.25% may produce a temporary increase in hepatic enzymes, it may not be prudent to not administer these solutions to patients with pre-existing hepatic conditions (Dagenais et al., 2008).

A systematic review by Hauser et al. examined dextrose (d-glucose) prolotherapy efficacy in the treatment of chronic musculoskeletal pain, searching databases from 1990 to January 2016. Fourteen RCTs, 1 case–control study, and 18 case series studies met the inclusion criteria. Pain conditions were clustered into tendinopathies, osteoarthritis (OA),...
spinal/pelvic, and myofascial pain. The RCTs were high quality and found that dextrose injection was superior to controls in Osgood-Schlatter disease, lateral epicondylitis of the elbow, traumatic rotator cuff injury, knee OA, finger OA, and myofascial pain; in biomechanical but not subjective measures in temporal mandibular joint; and comparable in a short-term RCT but superior in a long-term RCT in low back pain. Many observational studies were of high quality and reported consistent positive evidence in multiple studies of tendinopathies, knee OA, sacroiliac pain, and iliac crest pain that received RCT confirmation in separate studies. The reviewers concluded that overall, dextrose prolotherapy has been demonstrated to be efficacious and should be considered in patients who fail to respond to conservative therapies as a treatment for pain and dysfunction associated with chronic musculoskeletal conditions, particularly tendinopathies and OA. With inclusion limited to patients with pain >3–6 months in the reviewed studies, the efficacy of prolotherapy for acute (<3 months) musculoskeletal pain cannot be determined (2016).

Osteoarthritis (OA)

Knee
A partially blinded controlled trial was performed by Rabago et al. (2013) to assess the relationship between knee osteoarthritis (OA) relative to quality of life (QOL) and intra articular cartilage volume in participants treated with prolotherapy over a 52 week period. It was noted that prolotherapy is an injection therapy reported to improve knee OA-related QOL to a greater extent than blinded saline injections and at-home exercise, but its mechanism of action is unclear. It was noted that the prolotherapy showed improvement in the QOL in those with knee OA compared with the controlled group over the 52 week period. The study concluded that prolotherapy may have a pain-specific disease modifying effect, but still requires further research and testing.

In follow up to the above trial, Rabago et al. also assessed long-term effects of prolotherapy on knee pain, function and stiffness among adults with knee OA through a post clinical-trial, open-label follow-up study. Participants (n=65) received 3-5 monthly interventions and were assessed using the validated Western Ontario McMaster University Osteoarthritis Index, (WOMAC, 0-100 points), at baseline, 12, 26, 52 weeks, and 2.5 years. Progressive improvement in WOMAC scores were reported at all time intervals. The authors concluded that prolotherapy resulted in safe, significant, progressive improvement of knee pain, function and stiffness scores among most participants through a mean follow-up of 2.5 years and may be an appropriate therapy for patients with knee OA refractory to other conservative care (2015).

In an update to their 2007 Evidence-based Practice Center Systematic Review Protocol for the Treatment of Osteoarthritis of the Knee, the Agency for Healthcare Review and Quality (AHRQ) indicated that intra-articular injected agents such as prolotherapeutic substances are to be assessed for review in the next update (2016).

Fingers
Jahangiri et al. compared the advantages of prolotherapy in the treatment of first carpometacarpal osteoarthritis (OA) with those of corticosteroid local injection in a double-blind randomized clinical trial. Sixty participants (60 hands) with OA of the first carpometacarpal joint were assigned equally to 2 groups. For the corticosteroid group, after 2 monthly saline placebo injections, a single dose of 40 mg methylprednisolone acetate (0.5 ml) mixed with 0.5 ml of 2% lidocaine was injected. For the dextrose (DX) group, 0.5 ml of 20% DX was mixed with 0.5 ml of 2% lidocaine and the injection was repeated monthly for 3 months. Pain intensity, hand function and the strength of lateral pinch grip were measured at the baseline and at 1, 2, and 6 months post-treatment. The 2 groups were comparable at 2 months, but significantly different at 1 month (better results for corticosteroid), and at 6 months (more favorable outcome for DX). After 6 months of treatment, both DX and corticosteroid injection increased functional level, but DX seemed to be more effective. The authors concluded that for the long term, DX seemed to be more advantageous, while the 2 treatments were comparable in the short term. Further research with a large sample size is needed to compare possible complications of corticosteroid/lidocaine vs DX/lidocaine injections in the management of OA (2014).

Lateral Epicondylitis (LE)
Dong et al. (2015) conducted a systematic review and meta-analysis comparing many injection therapies (including prolotherapy) for lateral epicondylalgia. All of the injection treatments showed a trend towards better effects than placebo, and the study authors concluded prolotherapy’s superiority would need to be confirmed by more research.

Sims et al. (2014) conducted a systematic review of randomized controlled trials examining 11 non-surgical treatments for lateral epicondylitis which included prolotherapy. They concluded that the existing literature does not provide conclusive evidence that there is one preferred method of non-surgical treatment for this condition.

A pilot study (Rabago et al.) was conducted assessing dextrose prolotherapy (PrT) for chronic LE. The study design was a three-arm randomized controlled trial. Twenty-six adults (32 elbows) with chronic LE for 3 months or longer were randomized to ultrasound-guided PrT with dextrose solution, ultrasound-guided PrT with dextrose-morphuate sodium solution, or watchful waiting (“wait and see”). The primary outcome was the Patient-Rated Tennis Elbow Evaluation (PRTEE) (100 points) at 4, 8, and 16 weeks (all groups) and at 32 weeks (PrT groups). The secondary outcomes included pain-free grip strength and magnetic resonance imaging (MRI) severity score. The participants
receiving PrT with dextrose and PrT with dextrose-morrhae reported improved PRTEE composite and subscale scores at 4, 8, and/or 16 weeks compared with those in the wait-and-see group (P < 0.05). At 16 weeks, compared with baseline, the PrT with dextrose and PrT with dextrose-morrhae groups reported improved composite PRTEE scores by a mean (SE) of 18.7 (9.6; 41.1%) and 17.5 (11.6; 53.5%) points, respectively. The grip strength of the participants receiving PrT with dextrose exceeded that of the PrT with dextrose-morrhae and the wait and see at 8 and 16 weeks. There were no differences in MRI scores. Satisfaction was high; there were no adverse events. PrT resulted in safe, significant improvement of elbow pain and function compared with baseline status and follow-up data and the wait-and-see control group. This pilot study suggests the need for a definitive trial to validate these results across a larger population (2013).

**Groin Pain**

A case series by Topol and Reeves (2008) evaluated the use of prolotherapy in 75 athletes with chronic groin/abdominal pain. Participants received monthly injections of 12.5% dextrose in 0.5% lidocaine for 2 months. Average number of treatments received was 3 (range 1–6). Outcomes were measured using Visual Analog Scale (VAS) and Nirschl pain phase scale (NPPS). Seventy two athletes completed the full treatment. Follow-up occurred at an average of 26 months (range 6-73). VAS and NPPS improved 82% and 79% respectively. Sixty-six of 72 athletes returned to full sport, and all but 2 of the 66 athletes returned to full sport pain free. The authors found that 81% of the athletes had improvement in pain with 92% returning to unrestricted sports. The study is limited by small sample size and study design. Additional studies are needed to validate these results across a larger and more diverse population.

**Temporomandibular Joint (TMJ) Hypermobility**

Refaei et al. (2011) conducted a prospective, randomized, double-blind clinical study with 12 patients to assess the efficacy of dextrose prolotherapy for the treatment of TMJ hypermobility. While therapeutic results were promising, the authors concluded that continued research into prolotherapy's effectiveness with large sample sizes and long-term follow-up is needed.

**Lower Limb Tendinopathy**

A systematic review by Sanderson and Bryant (2015) evaluated the effectiveness and safety of prolotherapy injections for management of lower limb tendinopathy and fasciopathy. While no adverse events following prolotherapy injections were reported in any study in this review, the authors found limited evidence that prolotherapy injections are a safe and effective treatment for Achilles tendinopathy, plantar fasciopathy and Osgood-Schlatter disease. More robust research using large, methodologically-sound randomized controlled trials is required.

**Professional Societies**

**American Association of Orthopaedic Medicine (AAOM)**

In a position statement on Prolotherapy for the Treatment of Back Pain, the AAOM states that prolotherapy is a safe and efficacious therapy for the treatment of selected cases of low back pain and other chronic myofascial pain syndromes. This conclusion is based upon basic science data showing the effects of prolotherapy in animal models, clinical studies, a long history of clinical use, and increasingly widespread acceptance within the medical community. While they recognize that further basic science and clinical studies must be done, they are currently in process. The AAOM believes that prolotherapy is a safe, cost effective and efficacious therapy that can provide pain relief and return of function for many patients (2013).

There are multiple clinical trials studying prolotherapy for several musculoskeletal conditions which are actively recruiting participants or in progress. Additional information is available at www.clinicaltrials.gov.

**U.S. FOOD AND DRUG ADMINISTRATION (FDA)**

Two sclerosing agents have been approved by the FDA: sodium tetradecyl sulfate (Sotradecol®), and ethanolamine (Ethamolin®) for the treatment of varicose veins and esophageal varices. The agents used in the reviewed studies, such as dextrose and lidocaine, are approved for injection by the FDA but are not specifically approved for prolotherapy for joint and ligamentous injections, making such use off-label.

Another agent, sodium morrhuate (Scleromate®), is not currently listed as an approved sclerosing agent per the FDA.

Medicare does not cover prolotherapy, joint sclerotherapy or ligamentous injections with sclerosing agents. Refer to the National Coverage Determination (NCD) for Prolotherapy, Joint Sclerotherapy, and Ligamentous Injections with Sclerosing Agents (150.7). Also see the Local Coverage Determinations (LCDs) for Trigger Point Injections.


REFERENCES


POLICY HISTORY/REVISION INFORMATION

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<td>Updated supporting information to reflect the most current description of services, clinical evidence, FDA information, and references; no change to coverage rationale or lists of applicable codes</td>
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