

# PROLOTHERAPY FOR MUSCULOSKELETAL INDICATIONS

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Table of Contents	Page	Related Policies:
<a href="#">BENEFIT CONSIDERATIONS</a> .....	1	<a href="#">Bone or Soft Tissue Healing and Fusion Enhancement Products</a>
<a href="#">COVERAGE RATIONALE</a> .....	2	
<a href="#">APPLICABLE CODES</a> .....	2	
<a href="#">DESCRIPTION OF SERVICES</a> .....	2	
<a href="#">CLINICAL EVIDENCE</a> .....	2	
<a href="#">U.S. FOOD AND DRUG ADMINISTRATION CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS)</a> .....	6	
<a href="#">REFERENCES</a> .....	6	
<a href="#">POLICY HISTORY/REVISION INFORMATION</a> .....	8	

## **INSTRUCTIONS FOR USE**

*This Medical Policy provides assistance in interpreting UnitedHealthcare benefit plans. When deciding coverage, the enrollee specific document must be referenced. The terms of an enrollee's document (e.g., Certificate of Coverage (COC) or Summary Plan Description (SPD) and Medicaid State Contracts) may differ greatly from the standard benefit plans upon which this Medical Policy is based. In the event of a conflict, the enrollee's specific benefit document supersedes this Medical Policy. All reviewers must first identify enrollee eligibility, any federal or state regulatory requirements and the enrollee specific plan benefit 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.*

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## BENEFIT CONSIDERATIONS

### **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 (such as maternity benefits), 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 guideline, it is important to refer to the enrollee’s specific 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 Current Procedural Terminology (CPT<sup>®</sup>) codes and Healthcare Common Procedure Coding System (HCPCS) codes listed in this policy are for reference purposes only. Listing of a service code in this policy does not imply that the service described by this code is a covered or non-covered health service. Coverage is determined by the enrollee specific benefit 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 claims payment. Other policies and coverage determination guidelines may apply. This list of codes may not be all inclusive.

CPT Code	Description
0232T	Injection(s), platelet rich plasma, any site, including image guidance, harvesting and preparation when performed

HCPCS Code	Description
M0076	Prolotherapy

## 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, glycerine, dextrose-glycerine-phenol solution, zinc sulfate, fibrin glue, platelet-rich plasma or morrhuate sodium.

Prolotherapy is intended to increase joint stability by inducing an inflammatory process that mimics the natural healing process. The goal of prolotherapy is to promote joint and ligamentous stability and thereby reduce pain associated with abnormal joint motion. (Hayes, 2008)

## CLINICAL EVIDENCE

An evidence review of prolotherapy from the Veterans Administration Technology Assessment Program (VATAP) (Adams, 2008) stated, "Although proponents have advocated the use of prolotherapy for a range of indications, relatively few clinical uses have been studied systematically or published in the peer-reviewed literature. Results of the most recent systematic reviews are inconclusive for demonstrating the effectiveness of prolotherapy for treatment of musculoskeletal pain, and new evidence from case series would not alter these conclusions. The majority of published experimental studies have included conservative therapy with prolotherapy for relief of chronic low back pain, and to a lesser extent, osteoarthritis of the knee with varying results. Sample sizes have been insufficient on which to base national policy decisions."

### **Low Back Pain**

The evidence from published studies indicates that prolotherapy may provide very limited, short-term benefits for chronic back pain. While prolotherapy improved chronic low back pain 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 to 24 months. Prolotherapy may involve a single injection or a series of injections, often diluted with a local anesthetic.

[Prolotherapy for Musculoskeletal Indications: Medical Policy \(Effective 06/01/2014\)](#)

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 that prolotherapy is one of a number of treatments recommended for the treatment of chronic low-back pain. Prolotherapy has a long history of use, a reasonable but not proven theoretical basis, a low complication rate, and conflicting evidence of efficacy.

A systematic review by Rabogo et al. (2005) concluded that there are limited high-quality data supporting the use of prolotherapy in the treatment of musculoskeletal pain or sport-related soft tissue injuries. Their conclusion at that time did not support the use of prolotherapy in the treatment of musculoskeletal pain or sport-related soft due to the limited amount of high-quality data. Although positive results compared with controls have been reported in nonrandomized and randomized controlled trials, further investigation with high-quality randomized controlled trials with non-injection control arms in studies specific to sport-related and musculoskeletal conditions would be necessary to determine the efficacy of prolotherapy.

The largest and most rigorous trial of prolotherapy for nonspecific chronic low back pain was conducted by Yelland et al. (2004). One hundred ten patients were randomized to have repeated prolotherapy (20% glucose/0.2% lignocaine) or normal saline injections and then re-randomized to perform either flexion/extension exercises or normal activity over 6 months. At 1 and 2 year follow-up, there were no statistically significant differences between the groups in pain, disability, medication use, activity reduction due to back pain, or assessments of physical and mental quality of life. Likewise, flexion and extension exercises were not found to provide any significant benefit. There was no comparison to other types of treatments and therefore does not establish the efficacy of prolotherapy.

Ongley et al. (1987) conducted a randomized controlled trial (RCT) of prolotherapy as an adjunct to forceful physical manipulation versus placebo injection with non-forceful manipulation found that the treatment regimen including prolotherapy provided statistically significant improvements in pain and disability; however the results have not been replicated. In addition, this study has been criticized for its differences in treatment protocols other than the use of true versus placebo prolotherapy, raising significant doubt concerning the efficacy of prolotherapy.

A possible dose-response effect or the combination with other interventions such as spinal manipulation therapy may explain the conflicting results of RCTs. Two of the RCTs in which prolotherapy was administered using six weekly injections of 20 to 30 ml dextrose/glycerin/phenol/lidocaine with SMT and exercise had positive results, suggesting this particular intervention protocol is worth considering for patients with chronic low-back pain who are refractory to other approaches. At this time there is no evidence of efficacy for prolotherapy injections alone without co-interventions. Future studies are needed to support or refute the positive results obtained in some of the prior RCTs while addressing some of the methodological weaknesses by minimizing differences between the intervention and control groups. Additional studies are also needed to establish the safety of prolotherapy solutions, and determine the optimal dose and number of injection sessions required.

No clear patient selection criteria have been identified because efficacy of the therapy has not been established. In general, prolotherapy is contraindicated in patients with metastatic cancer, nonmusculoskeletal pain, spinal anatomical defects, systemic inflammation, morbid obesity, bleeding disorders, low pain threshold, inability to perform post-treatment exercises, whole body pain, or hepatic conditions (Dagenais et al., 2008).

In a Cochrane Review on prolotherapy injections for chronic low-back pain, the authors 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. (Dagenais et al., 2007)

### **Osteoarthritis**

A partially blinded controlled trial was performed by Rabago et al (2013) to assess the relation between knee osteoarthritis specifically related to quality of life 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 KOA-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 quality of life those with knee osteoarthritis 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 at this time.

A limited short-term benefit of prolotherapy was observed for osteoarthritis in two randomized controlled trials that evaluated prolotherapy versus placebo prolotherapy for osteoarthritis of the knee or the thumb and finger joints. However, the improvements were small and the studies did not include follow-up and it is therefore not known whether the treatment effect was maintained. The larger of these studies enrolled 68 patients who had 111 osteoarthritic knees. Although this study found that prolotherapy provided an improvement in all of the pain, swelling, knee buckling, and flexion outcome measures combined, most of the improvements were small and the statistical significance of differences between the treatment and control groups in individual outcome measures was not reported.

Reeves and Hassanein (2000) enrolled 27 patients with 150 osteoarthritic finger joints and found that compared with the control group, patients randomized to prolotherapy had statistically significant improvements in flexion and pain during movement; however, there were no significant improvements in resting pain or grip pain.

The clinical evidence was reviewed on March 5, 2013 with no additional information identified.

### **Lateral Epicondylitis (LE)**

Rabago et al. (2009) completed a systematic review of the existing evidence for prolotherapy, polidocanol, autologous whole blood, and platelet-rich plasma (PRP) injection therapies for lateral epicondylitis (LE). This review included 5 prospective case series and 4 controlled trials (3 prolotherapy, 2 polidocanol, 3 autologous whole blood and 1 PRP) which suggested each of the 4 therapies is effective for LE. The authors concluded that there is strong pilot-level evidence supporting the use of prolotherapy, polidocanol, autologous whole blood, and PRP injections. However, rigorous studies of sufficient sample size are needed to determine long-term safety and effectiveness, and whether these techniques can play a definitive role in the management of LE and other tendonopathies.

Scarpone et al. (2008) conducted a double blind randomized controlled trial on 20 patients to assess whether prolotherapy improves elbow pain, grip strength and isometric resistance strength in patients with lateral epicondylitis. Each patient received blinded injections of either a sodium morrhuate solution (study group) or normal saline (control group) over an 8-week period with in office follow-up occurring over 16 weeks and a final telephone interview at one year. The primary outcome measured was elbow pain with grip strength and isometric resistance strength as secondary outcomes. Elbow pain and resistance strength showed improvement in the study group, while grip strength showed no significant change between the 2 groups. The authors conclude that prolotherapy decreased elbow pain and improved extension in patients with lateral epicondylitis. Grip strength improved in both groups. However, the study is limited by small sample size. Additional studies are needed to validate results across a larger population.

A pilot study (Rabago et al 2013) was conducted assessing dextrose prolotherapy for chronic lateral epicondylitis. The study design was three-arm randomized controlled trial. Twenty-six adults (32 elbows) with chronic lateral epicondylitis for 3 mos or longer were randomized to ultrasound-guided PrT with dextrose solution, ultrasound-guided PrT with dextrose-morrhuate sodium solution, or watchful waiting ("wait and see"). The primary outcome was the Patient-Rated Tennis Elbow Evaluation (100 points) at 4, 8, and 16 wks (all groups) and at 32 wks (PrT groups). The secondary outcomes included pain-free grip strength and magnetic resonance imaging severity score.

The participants receiving PrT with dextrose and PrT with dextrose-morrhuate reported improved Patient-Rated Tennis Elbow Evaluation composite and subscale scores at 4, 8, and/or 16 wks compared with those in the wait-and-see group ( $P < 0.05$ ). At 16 wks, compared with baseline, the PrT with dextrose and PrT with dextrose-morrhuate groups reported improved composite Patient-Rated Tennis Elbow Evaluation 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-morrhuate and the wait and see at 8 and 16 wks ( $P < 0.05$ ). There were no differences in magnetic resonance imaging 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.

### **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 improved by 82% and NPPS improved 79%. 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.

The clinical evidence was reviewed on March 18, 2014 with no additional information identified.

### **Professional Societies**

**European Commission Research Directorate General (ECRDG):** A 2004 ECRDG Working Group that developed guidelines for the treatment of chronic low back pain concluded that there was strong evidence that prolotherapy is not an effective treatment for nonspecific chronic low back pain. Therefore, the Working Group recommended against use of prolotherapy for this disorder.



**American Association of Orthopaedic Medicine (AAOM):** In a 2006 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.

**American College of Occupational and Environmental Medicine (ACOEM):** A 2007 ACOEM guideline on injection therapy does not recommend prolotherapy injections for acute, subacute, chronic low back pain or radicular pain syndrome.

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

Two sclerosing agents have been approved by the FDA: sodium tetradecyl sulfate (Sotradecol<sup>®</sup>), and ethanolamine (Ethamolin<sup>®</sup>) 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, morrhuate sodium (Scleromate<sup>®</sup>), is not currently listed as an approved sclerosing agent per the FDA.

Additional information, under active ingredient name sodium tetradecyl sulfate and ethanolamine, is available at: <http://www.fda.gov/cder/ob/default.htm>. Accessed March 18, 2014

### CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS)

Medicare does not cover Prolotherapy, Joint Sclerotherapy and Ligamentous Injections with Sclerosing Agents as the medical effectiveness of these modalities has not been verified by scientifically controlled studies. Refer to the National Coverage Determination (NCD) for [Prolotherapy, Joint Sclerotherapy, and Ligamentous Injections with Sclerosing Agents \(150.7\)](#). Local Coverage Determinations (LCDs) do not exist at this time. (Accessed March 18, 2014)

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**POLICY HISTORY/REVISION INFORMATION**

Date	Action/Description
06/01/2014	<ul style="list-style-type: none"> <li>• Reorganized policy content</li> <li>• Added benefit considerations language for <i>Essential Health Benefits for Individual and Small Group</i> plans to indicate:               <ul style="list-style-type: none"> <li>○ 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”)</li> <li>○ 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 (such as maternity benefits), the ACA requires all dollar limits on those benefits to be removed on all Grandfathered and Non-Grandfathered plans</li> <li>○ The determination of which benefits constitute EHBs is made on a state by state basis; as such, when using this guideline, it is important to refer to the enrollee’s specific plan document to determine benefit coverage</li> </ul> </li> <li>• Updated coverage rationale; added language to indicate the unproven service is “not medically necessary”</li> <li>• Updated supporting information to reflect the most current clinical evidence and references</li> <li>• Archived previous policy version 2013T0498H</li> </ul>