Policy Statement

Prolotherapy is considered investigational as a treatment of musculoskeletal pain.

Policy Guidelines

Coding
The following HCPCS code is specific to prolotherapy:
- M0076: Prolotherapy

However, providers may be using one of the following nonspecific CPT codes:
- 20550: Injection(s); single tendon sheath, or ligament, aponeurosis (e.g., plantar “fascia”)
- 20551: Injection(s); single tendon origin/insertion
- 20552: Injection(s); single or multiple trigger point(s), 1 or 2 muscle(s)
- 20999: Unlisted procedure, musculoskeletal system, general
- 27096: Injection procedure for sacroiliac joint, anesthetic/steroid, with image guidance (fluoroscopy or CT) including arthrography when performed
- 64490: Injection(s), diagnostic or therapeutic agent, paravertebral facet (zygapophyseal) joint (or nerves innervating that joint) with image guidance (fluoroscopy or CT), cervical or thoracic; single level
- 64491: Injection(s), diagnostic or therapeutic agent, paravertebral facet (zygapophyseal) joint (or nerves innervating that joint) with image guidance (fluoroscopy or CT), cervical or thoracic; second level (List separately in addition to code for primary procedure)
- 64492: Injection(s), diagnostic or therapeutic agent, paravertebral facet (zygapophyseal) joint (or nerves innervating that joint) with image guidance (fluoroscopy or CT), cervical or thoracic; third and any additional level(s) (List separately in addition to code for primary procedure)
- 64493: Injection(s), diagnostic or therapeutic agent, paravertebral facet (zygapophyseal) joint (or nerves innervating that joint) with image guidance (fluoroscopy or CT), lumbar or sacral; single level
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- 64495: Injection(s), diagnostic or therapeutic agent, paravertebral facet (zygapophyseal) joint (or nerves innervating that joint) with image guidance (fluoroscopy or CT), lumbar or sacral; third and any additional level(s) (List separately in addition to code for primary procedure)

Description

Prolotherapy describes a procedure intended for healing and strengthening ligaments and tendons by injecting an agent that induces inflammation and stimulates endogenous repair mechanisms. Prolotherapy may also be referred to as proliferant injection, prolo, joint sclerotherapy, regenerative injection therapy, growth factor stimulation injection, or nonsurgical tendon, ligament, and joint reconstruction.
Related Policies

- Autologous Platelet-Derived Growth Factors for Wound Healing and Other Non-Orthopedic Conditions

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

Sclerosing agents have been approved by the U.S. Food and Drug Administration (FDA) for use in treating spider and varicose veins. These sclerosing agents include Asclera® (polidocanol), Varithena® (an injectable polidocanol foam), Sotradecol® (sodium tetradecyl sulfate), Ethamolin® (ethanolamine oleate), and Scleromate® (sodium morrhuate). These agents are not currently approved as joint and ligamentous sclerosing agents.

Rationale

Background

The goal of prolotherapy is to promote tissue repair or growth by prompting the release of growth factors, such as cytokines, or by increasing the effectiveness of existing circulating growth factors. The mechanism of action is not well-understood but may involve local irritation and/or cell lysis. Agents used with prolotherapy have included zinc sulfate, psyllium seed oil, combinations of dextrose, glycerin, and phenol, or dextrose alone, often combined with a local anesthetic. Polidocanol, sodium morrhuate, and vascular sclerosants have also been used to sclerose areas of high intratendinous blood flow associated with tendinopathies. Prolotherapy typically involves multiple injections per session conducted over a series of treatment sessions.

A similar approach involves the injection of autologous platelet-rich plasma, which contains a high concentration of platelet-derived growth factors. Treatment of musculoskeletal pain conditions (e.g., tendinopathies) with platelet-rich plasma is discussed Blue Shield of California Medical Policy: Autologous Platelet-Derived Growth Factors for Wound Healing and Other Non-Orthopedic Conditions.

Literature Review

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function—including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to 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 a technology, 2 domains are examined: the relevance and the 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.

Prolotherapy has been investigated as a treatment of various etiologies of musculoskeletal pain, including arthritis, degenerative disc disease, fibromyalgia, tendinitis, and plantar fasciitis. As with any therapy for pain, a placebo effect is anticipated, and thus randomized placebo-controlled trials are necessary.

When this evidence review was created in 1997, there was extensive literature on prolotherapy; however, literature searches have identified only a randomized placebo-controlled trials.

**Prolotherapy**

**Clinical Context and Therapy Purpose**

The purpose of prolotherapy in patients who have musculoskeletal pain, osteoarthritic pain, or tendinopathies of the upper or lower limbs is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does the use of prolotherapy improve the net health outcome in those who suffer from musculoskeletal pain, osteoarthritic pain, or tendinopathies of the upper or lower limbs?

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

**Patients**

The relevant populations of interest are individuals who suffer from musculoskeletal pain, osteoarthritic pain, or upper- or lower-limb tendinopathies.

**Interventions**

The therapy being considered is prolotherapy.

**Comparators**

The following therapies and practices are currently being used to treat musculoskeletal pain, osteoarthritic pain, and upper- or lower-limb tendinopathies: observation and other conservative therapies.

**Outcomes**

The general outcomes of interest are reductions in pain and medication use, improvements in function, and treatment-related adverse events (mostly mild but in rare instances serious).

**Timing**

Varying by condition, injections are administered over a series of sessions, which can last from several weeks to months.

**Setting**

Injections are administered in an outpatient setting.
Chronic Neck and Back Pain

Systematic Reviews

A Cochrane review by Dagenais et al (2007) evaluated prolotherapy for chronic low back pain and concluded that “When used alone, prolotherapy is not an effective treatment for chronic low back pain.” Reviewers also concluded that, although confounded by cointerventions and heterogeneity of studies, “When combined with spinal manipulation, exercise, and other interventions, prolotherapy may improve chronic low-back pain and disability.”

Another systematic review by Dagenais et al (2008) of the same 5 studies included in the Cochrane review and by one of the same authors concluded that despite its use for more than 50 years, there is no evidence of efficacy for prolotherapy injections alone for chronic low back pain. The same evidence was evaluated in a systematic review conducted by Chou et al (2009) for the American Pain Society. In this case, reviewers also concluded that prolotherapy was ineffective when used alone to manage chronic low back pain.

Two 2005 reviews also noted that there were limited high-quality data to support prolotherapy and that the great variation in injection and treatment protocols limited interpretation of the data.

A Cochrane review by Yelland et al (2004) also concluded that prolotherapy injections had not been proven to be more effective than placebo injections.

Randomized Controlled Trials

Three randomized trials were identified that focused on the use of injections of dextrose, glycerin, and phenol as a treatment for low back pain. Yelland et al (2004) reported on a partially blinded RCT of prolotherapy injections, saline injections, and exercises for chronic low back pain in 110 subjects. While decreases in pain and disability were noted in all study groups, there were no significant differences between treatment groups at 12 and 24 months. Therefore, the effects of prolotherapy did not significantly exceed placebo effects.

Klein et al (1993) reported on a trial that randomized 79 patients with low back pain to a series of 6 weekly injections using either saline or a proliferant solution of dextrose, glycerin, and phenol. Thirty of the 39 patients assigned to the proliferant group achieved a 50% or greater diminution in pain compared with 21 of the 40 in the placebo group. While the incremental benefit of the treatment group was statistically significant (p = 0.04), blinding of the treatment groups was not maintained, because those assigned to the proliferant group experienced a clinically recognizable local inflammatory response.

Ongley et al (1987) reported on a trial of 81 patients with low back pain who were randomized to spinal manipulation plus prolotherapy or a control group that received less forceful spinal manipulation, less local anesthesia, and placebo injections of saline. Although improved responses were reported for the treatment group, it was not possible to evaluate the contribution of prolotherapy compared with the impact of the different types of spinal manipulation.

Nonrandomized Studies

Dagenais et al (2006) also conducted a survey of practitioners of prolotherapy for back and neck pain. Completed surveys (n=171, 50% response rate) revealed that practitioners had a median of 10 years of experience, with a median 2000 treatments in 500 patients. About 500 adverse events (25% of treatments) were reported; 69 (14% of patients) required hospitalization. Adverse events included spinal disc injury, hemorrhage, infection, nerve damage, pneumothorax, spinal headache, spinal cord insult, and systemic reactions.
Other Musculoskeletal Pain

Randomized Controlled Trials

A trial by Kim et al (2010) compared intra-articular prolotherapy with intra-articular corticosteroid injection for sacroiliac pain. The double-blind, randomized study included 48 patients with sacroiliac joint pain lasting 3 months or more, confirmed by 50% or more improvement in response to local anesthetic block. The injections were performed on a biweekly schedule (maximum of 3 injections) under fluoroscopic guidance with confirmation of the intra-articular location with an arthrogram. Pain and disability scores were assessed at baseline, 2 weeks, and monthly after completion of treatment. At 2 weeks after treatment, all patients met the primary outcome measure of 50% or more reduction in pain scores, and there was no significant difference between groups. The numeric rating scale score for pain was reduced from 6.3 to 1.4 in the prolotherapy group and from 6.7 to 1.9 in the steroid group. The Oswestry Disability Index score decreased from 33.9 to 11.1 in the prolotherapy group and from 35.7 to 15.5 in the steroid group. Kaplan-Meier survival analysis showed a significantly greater percentage of patients with sustained relief following prolotherapy. At 6 months after treatment, 63.6% of patients in the prolotherapy group reported 50% or more improvement from baseline compared with 27.2% of the steroid group. At 15 months after treatment, 58.7% of patients in the prolotherapy group reported 50% or more relief compared with 10.2% of the steroid group. Key differences between this and other studies on prolotherapy were the selection of patients using a diagnostic sacroiliac joint block and the use of an arthrogram to confirm the location of the injection. Additional trials are needed to confirm the safety and efficacy of this procedure.

Prospective Studies

Reeves and Hassanein (2003) reported on a study of dextrose prolotherapy for anterior cruciate ligament laxity. Of 16 evaluable patients, statistically significant improvements were found at 6, 12, and 36 months in anterior cruciate ligament laxity, pain, swelling, and knee range of motion. However, this was a small, nonrandomized trial and, as previously noted, without placebo control, the extent to which improvements with prolotherapy exceeded those associated with a placebo could be determined.

Osteoarthritis

Jahangiri et al (2014) reported on a double-blind, randomized trial that compared prolotherapy with corticosteroid for the treatment of osteoarthritis in the first carpometacarpal joint. Sixty patients were randomized to 3 monthly prolotherapy injections or 2 monthly saline injections plus a corticosteroid injection in the third month. The groups were comparable at baseline, with a visual analog scale (VAS) score for pain on pressure of 6.7 in the prolotherapy group and 6.4 in the corticosteroid group. At the 6-month follow-up, pain had decreased more (by \( \approx 2 \) cm on the VAS; VAS final score, <2) in the prolotherapy group compared with the corticosteroid-treated group (\( p<0.001 \)). Pain on movement and hand function had also improved to a greater extent in the prolotherapy group.

Rabago et al (2013) reported on an RCT of prolotherapy for knee osteoarthritis. This trial was supported by the National Center for Complementary and Alternative Medicine. Ninety patients were randomized to blinded injections (3-5 treatments with dextrose prolotherapy or saline) or at-home exercise. All 3 groups showed improvements on the composite Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), with significantly greater improvement in the prolotherapy group (15.3 points) than in the saline and exercise groups (7.6 and 8.2 points, respectively). At 52 weeks, 50% of prolotherapy patients achieved the minimum clinically important difference of a 12-point change in WOMAC score, compared with 30% of saline-treated patients and 24% of exercise participants. Knee pain scores also improved more in the prolotherapy group. Rabago et al (2015) reported on a 2.5-year telephone follow-up from prolotherapy-treated patients in their randomized trial and from 2 uncontrolled open-label studies. The 3 prolotherapy groups were comparable, having undergone similar treatment courses and showing similar improvements in WOMAC score at 52 weeks (15.3, 12.4, 15.9 points, respectively). At a mean 2.5-year follow-up (range, 1.5-3.5 years), the 65 patients who agreed to participate in this follow-up study had a mean 20.9-point improvement in the WOMAC score.
There is a risk of bias due to the open-label design and the relatively high proportion (10%) of prolotherapy-treated patients who declined to participate in the telephone interview.

Reeves and Hassanein (2000) reported on 2 trials that used dextrose to treat osteoarthritis of the knee. The first trial randomized 68 patients with 111 osteoarthritic knees to either 3 bimonthly injections of dextrose or placebo. The patients were evaluated with a VAS for pain and swelling, frequency of leg buckling, goniometrically measured flexion, and radiographic measures of joint narrowing. As presented, the data suggested a significant improvement in both the placebo and the treatment groups, but it is difficult to determine the comparative magnitude of improvement between the groups. For example, for the various outcome measures of pain, it appears that there were probably no clinically significant incremental effects of prolotherapy compared with the placebo group. However, for other nonpain outcomes (i.e., swelling, buckling, flexion range), prolotherapy might have been associated with a significant incremental improvement. The various outcome measures were combined and assessed using a Hotelling multivariate analysis. With this statistical measurement, prolotherapy demonstrated a statistically superior overall effect (p=0.015) compared with the control group. It should be recognized that the statistical significance of this measure was most likely due to the improvements in the nonpain symptoms (i.e., swelling, buckling, flexion range). In summary, it is uncertain whether the incremental improvement in the non-pain-related outcomes of the prolotherapy group compared with the control group is clinically significant.

In a similarly designed study, Reeves and Hassanein (2000) also assessed the effectiveness of prolotherapy as a treatment of osteoarthritic thumb and finger joints. Twenty-seven patients with 150 osteoarthritic joints were randomized to 3 bimonthly injections of dextrose or water. Patients were evaluated with both VAS for pain and goniometric assessment of joint movement. Because patients had a variable number of joints injected (range, 1-22), the VAS score for every symptomatic joint in each patient was added together for a total and divided by the number of symptomatic joints to provide an average joint pain score for each patient. There were improvements in pain scores in both the placebo and the treatment groups, but the incremental improvement of the treatment group compared with the placebo group was not statistically significant. Regarding flexion, the treatment group reported a statistically significant improvement (p=0.043), while the placebo group reported a greater, statistically significant decrease (p=0.011). Therefore, the statistically significant difference in flexion between the groups (p=0.003) was primarily related to the decrease in the control group, with a smaller contribution related to the positive response in the treatment group. In summary, the clinical significance of an isolated finding of improved flexion without a corresponding significant improvement in pain is uncertain.

**Tendinopathies of the Upper and Lower Limbs**

**Lateral Epicondylitis**

*Systematic Reviews*

A systematic review by Rabago et al (2009) evaluated injection therapies for lateral epicondylitis (tennis elbow); 2 RCTs and a prospective case series on prolotherapy were included. One of the randomized trials was referenced as a report from a 2006 conference on complementary and alternative medicine; no authors were listed in the reference, and the trial does not appear to be published in the peer-reviewed literature. The second double-blind, randomized placebo-controlled trial by Scarpone et al (2008) involved 20 patients who had elbow pain for at least 6 months and failure of conservative therapy (rest, physical therapy, nonsteroidal anti-inflammatory drugs, 2 corticosteroid injections) and who received 3 treatments (over 8 weeks) of prolotherapy or saline injection. There was a significant reduction in pain with prolotherapy injection (5.1 to 0.5 on a Likert scale) compared with saline injection (4.5 to 3.5). Isometric strength also improved (13 to 31 lb vs 10 to 11 lb, respectively), but there was no difference in grip strength between both groups.
Randomized Controlled Trials
A small (17 subjects) double-blind, randomized trial comparing prolotherapy with corticosteroid injections for chronic lateral epicondylitis was reported by Carayannopoulos et al (2011). Each subject received an injection at baseline followed by a second injection at 1 month. VAS for pain, quadruple VAS, and Disabilities of the Arm, Shoulder, and Hand questionnaire (DASH) were measured at baseline and at 1, 3, and 6 months. Changes of 2 for in VAS score and 12 for in DASH score were considered clinically significant. Per protocol analysis showed a significant improvement in VAS and DASH scores at both 3 months (2.38 and 19.89) and 6 months (2.63 and 21.76), both respectively, for the prolotherapy group, while the corticosteroid group showed significant improvement for DASH scores at 3 months (13.33) and 6 months (15.56). The trial was underpowered to detect a significant difference between the prolotherapy and corticosteroid groups for change in VAS, quadruple VAS, or DASH scores.

Achilles Tendonitis
Yelland et al (2011) reported a multicenter randomized trial of prolotherapy or exercises for Achilles tendonitis in 43 patients. Inclusion criteria were diagnosis of unilateral or bilateral mid-portion Achilles tendinosis with pain between 2 cm and 7 cm proximal to the calcaneal attachment in adults older than 18 years with activity-related pain for at least 6 weeks. The sample size was limited by the available resources and slow recruitment rate, resulting in 15 participants in the eccentric loading exercise group, 14 in the prolotherapy group, and 14 in the combined treatment group. Randomization was conducted by a central site and resulted in a lower median duration of pain in the combined treatment group (6 months) than in the exercise alone (21 months) or prolotherapy alone (24 months) groups. An average of 4.4 injections per treatment was directed at tender points in the subcutaneous tissues adjacent to the affected tendon, with 4 to 12 weekly treatments until participants attained pain-free activity or requested to cease treatment. Participants were instructed to perform eccentric loading exercises. Clinical reviews were performed at 3, 6, and 12 weeks to check technique and progress. Mean increases in the validated Victorian Institute of Sport Assessment–Achilles (VISA-A) score were 23.7 for exercise alone, 27.5 for prolotherapy alone, and 41.1 for the combined treatment. At 6 weeks and 12 months, these increases were significantly greater for combined treatment (exercise and prolotherapy) than for exercise alone. The predefined minimum clinically important increase of 20 points or more on the VISA-A was obtained by 12 subjects in the combined treatment group and 11 each in the exercise alone and prolotherapy alone groups; the difference was not statistically significant. The percentage of patients achieving full recovery (VISA-A score of ≥90 at 12 months) was 53% for exercise alone, 71% for prolotherapy alone, and 64% for the combined treatment group; but these differences were not significant. This trial was limited by the combination of a small number of subjects per group, unequal durations of pain in the treatment groups at baseline, and minimal differences in the number of patients showing recovery (11/14 vs 12/15, respectively).

Summary of Evidence
For individuals who have musculoskeletal pain (e.g., chronic neck, back pain), osteoarthritic pain, or tendinopathies of the upper or lower limbs who receive prolotherapy, the evidence includes small randomized trials with inconsistent results. Relevant outcomes are symptoms, functional outcomes, and quality of life. The strongest evidence evaluates the use of prolotherapy for the treatment of osteoarthritis, but the clinical significance of the therapeutic results is uncertain. The evidence is insufficient to determine the effects of the technology on health outcomes.

Supplemental Information
Practice Guidelines and Position Statements

American Association of Orthopedic Medicine
The American Association of Orthopedic Medicine currently has a recommendation posted online for the use of prolotherapy for back pain. The Association has indicated that
“...prolotherapy should be considered a valid treatment option in a selected group of chronic low back pain patients.”

**U.S. Preventive Services Task Force Recommendations**
Not applicable.

**Medicare National Coverage**
The Centers for Medicare & Medicaid currently do not cover prolotherapy, joint sclerotherapy, and ligamentous injections with sclerosing agents.23

**Ongoing and Unpublished Clinical Trials**
Some currently unpublished trials that might influence this review are listed in Table 1.

### Table 1. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
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<td>Comparison of Conservative Methods for the Treatment of Lateral Epicondylitis: A Randomized, Prospective Study</td>
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<td>Treatment of Temporomandibular Dysfunction with Hypertonic Dextrose Injection: A Randomized Clinical Trial Efficacy</td>
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<td>Prolotherapy in the Treatment of Rotator Cuff Tendinopathy, a Randomized Double-blind Placebo-controlled Study</td>
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<td>Jun 2013 (completed)</td>
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</table>

NCT: national clinical trial.

### References


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**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.
The following services may be considered investigational.

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### Definitions of Decision Determinations

**Medically Necessary:** A treatment, procedure, or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.

**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. Please call (800) 541-6652 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.