



**BlueCross BlueShield
of Alabama**

Name of Policy:

Prolotherapy

Policy #: 235
Category: Surgery

Latest Review Date: August 2014
Policy Grade: D

Background/Definitions:

As a general rule, benefits are payable under Blue Cross and Blue Shield of Alabama health plans only in cases of medical necessity and only if services or supplies are not investigational, provided the customer group contracts have such coverage.

The following Association Technology Evaluation Criteria must be met for a service/supply to be considered for coverage:

- 1. The technology must have final approval from the appropriate government regulatory bodies;*
- 2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes;*
- 3. The technology must improve the net health outcome;*
- 4. The technology must be as beneficial as any established alternatives;*
- 5. The improvement must be attainable outside the investigational setting.*

Medical Necessity means that health care services (e.g., procedures, treatments, supplies, devices, equipment, facilities or drugs) that a physician, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury or disease or its symptoms, and that are:

- 1. In accordance with generally accepted standards of medical practice; and*
- 2. Clinically appropriate in terms of type, frequency, extent, site and duration and considered effective for the patient's illness, injury or disease; and*
- 3. Not primarily for the convenience of the patient, physician or other health care provider; and*
- 4. Not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.*

Description of Procedure or Service:

Prolotherapy describes a procedure 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.

The goal of prolotherapy is to promote tissue repair or growth by prompting release of growth factors, such as cytokines, or 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 dextrose, glycerine, and phenol, or dextrose alone, often combined with a local anesthetic. Polidocanol and sodium morrhuate, 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 (PRP), which contains a high concentration of platelet derived growth factors. Treatment of musculoskeletal pain conditions (e.g., tendinopathies) with PRP is discussed in policy #241 Recombinant and Autologous Platelet-Derived Growth Factors as a Treatment of Wound Healing and Other Conditions.

Policy:

Prolotherapy does not meet Blue Cross and Blue Shield of Alabama's medical criteria for coverage and is considered **investigational** as a treatment of musculoskeletal pain or other conditions.

Blue Cross and Blue Shield of Alabama does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Cross and Blue Shield of Alabama administers benefits based on the member's contract and corporate medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

Key Points:

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 to investigate the extent of the placebo effect and to determine whether any improvement with prolotherapy exceeds that associated with a placebo. When this policy was created, there was extensive literature regarding prolotherapy; however, a literature search revealed only four randomized placebo-controlled trials. The literature has been updated

periodically with searches of the MEDLINE database. The most recent update was performed through July 2014. Key studies to date are described below.

Chronic Neck and Back Pain

In 2004, a Cochrane review concluded that prolotherapy injections have not been proven to be more effective than placebo injections. Two 2005 reviews also noted that there was limited high-quality data to support prolotherapy and that the great variation in injection and treatment protocols limited interpretation of the data. An updated 2007 Cochrane review on prolotherapy for chronic low back pain concluded that “When used alone, prolotherapy is not an effective treatment for chronic low-back pain.” The authors also concluded that, although confounded by co-interventions and heterogeneity of studies, “When combined with spinal manipulation, exercise, and other interventions, prolotherapy may improve chronic low-back pain and disability.” A 2008 systematic review (of the same five 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 2009 systematic review conducted for the American Pain Society. The authors of this review concluded that prolotherapy was found to be ineffective when used alone for chronic low back pain.

Three randomized trials were identified that focused on the use of injections of dextrose, glycerin, and phenol as a treatment of low back pain. In 1987, Ongley et al reported on a trial of 81 patients with low back pain who were randomly assigned to receive spinal manipulation plus prolotherapy compared to 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 is not possible to isolate the possible contribution of the prolotherapy compared to the impact of the different types of spinal manipulation.

In 1993, Klein et al reported on a trial that randomly assigned 79 patients with low back pain to receive a series of six weekly injections using either saline or a proliferant solution of dextrose, glycerine, and phenol. Thirty of the 39 patients assigned to the proliferant group achieved a 50% or greater diminution in pain compared to 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, since those assigned to the proliferant group experienced a clinically recognizable local inflammatory response.

In 2004, Yelland et al reported on a randomized, partially blinded, controlled trial on 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 found between treatment groups at 12 and 24 months. Therefore, the effects of prolotherapy did not significantly exceed placebo effects.

Dagenais et al 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 ten years of experience, with a median 2,000 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. The efficacy of prolotherapy for chronic neck and back pain has not been demonstrated; this procedure is considered investigational.

Osteoarthritis

Rabago et al reported a randomized controlled trial of prolotherapy for knee osteoarthritis in 2013. This study was supported by the National Center for Complementary and Alternative Medicine (NCCAM). Ninety patients were randomized to blinded injections (3-5 treatments with dextrose prolotherapy or saline) or at-home exercise. All three 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) compared to saline and exercise groups (7.6, and 8.2 points, respectively). At 52 weeks, 50% of prolotherapy patients achieved the minimum clinically important difference (MCID) of a 12-point change in WOMAC, compared to 30% of saline-treated patients and 24% of exercise participants. Knee pain scores also improved more in the prolotherapy group.

In 2000, Reeves and Hassanein reported on two trials that used dextrose for the treatment of osteoarthritis. The first trial randomly assigned 68 patients with 111 osteoarthritic knees to receive either three bimonthly injections of dextrose or placebo. The patients were evaluated with a visual analog scale (VAS) for pain and swelling, frequency of leg buckling, goniometrically measured flexion, and radiographic measures of joint narrowing. As the data are presented, it is clear that there was significant improvement in both the placebo and treatment groups, but it is difficult to determine the comparative magnitude of improvement between the two groups. For example, for the various outcome measures of pain, it appears that there are probably no clinically significant incremental effects of prolotherapy compared to the placebo group. However, for other non-pain outcomes, i.e., swelling; buckling; and flexion range, prolotherapy may be 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 to the control group. It should be recognized that the statistical significance of this measure is most likely due to the improvements in the non-pain symptoms (i.e., swelling, buckling, and flexion range). In summary, it is not known whether the incremental improvement in the non-pain-related outcomes of the prolotherapy group compared to the control group is clinically significant.

In a similarly designed study, the same investigators studied the effectiveness of prolotherapy as a treatment of osteoarthritic thumb and finger joints. A total of 27 patients with 150 osteoarthritic joints were randomly assigned to receive three bimonthly injections of either dextrose or water. Patients were evaluated with both VAS for pain and goniometric assessment of joint movement. Since patients had a variable number of joints injected (ranging from 1 to 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 treatment groups, but the incremental improvement of the treatment group compared to the placebo group did not reach statistical significance. In terms of 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 two 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

A 2009 systematic review evaluated injection therapies for lateral epicondylitis (tennis elbow); two randomized controlled trials (RCTs) and one 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 are listed in the reference, and the study does not appear to be available in the peer-reviewed published literature. The second randomized double-blind placebo-controlled trial involved 20 patients who had elbow pain for at least six months and failure of conservative therapy (rest, physical therapy, nonsteroidal anti-inflammatory drugs, and two corticosteroid injections) to three treatments (over eight weeks) of prolotherapy or saline injection. There was a significant improvement in pain with prolotherapy injection (from 5.1 to 0.5 on a Likert scale) in comparison 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 the two conditions. The authors indicated that this is the first randomized trial of prolotherapy for tendinopathy and that additional research with a larger study population is needed.

A small (17 subjects) randomized double-blind trial of prolotherapy versus corticosteroid injections for chronic lateral epicondylitis was reported in 2011. Each subject received an injection at baseline followed by a second injection at one month. VAS for pain, quadruple VAS (QVAS), and Disabilities of the Arm, Shoulder, and Hand questionnaire (DASH) were measured at baseline and at one, three, and six months. A change of 2 for VAS and 12 for DASH was considered clinically significant. Per protocol analysis showed a significant improvement in VAS and DASH at both three (2.38 and 19.89) and six months (2.63 and 21.76, both respectively) for the prolotherapy group, while the corticosteroid group showed significant improvement on the DASH at 3 (13.33) and six months (15.56). The study was underpowered to detect a significant difference between the prolotherapy and corticosteroid groups for change in VAS, QVAS, or DASH. Larger controlled trials are needed.

Achilles Tendonitis

Yelland et al, an author of Cochrane reviews on this topic, 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 and 7 cm proximal to the calcaneal attachment in adults older than 18 years with activity-related pain for at least six 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 (six 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 four to twelve weekly treatments until participants attained pain-free

activity or requested to cease treatment. The participants were instructed to perform eccentric loading exercises twice daily in three sets of 15 repetitions with the knee straight and three sets of 15 repetitions with the knee bent for a period of 12 weeks, with the load progressively increased by adding weights to a backpack. 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 six 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. This was not significantly different. The percentage of patients achieving full recovery (VISA-A score of 90 or above 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. Although the authors concluded that prolotherapy may be a cost-effective method to speed recovery in patients with Achilles tendonitis, this study is limited by the combination of a small number of subjects per group, unequal duration of pain in the treatment groups at baseline, and minimal differences in the number of patients showing recovery (11 vs. 12, of 14 or 15, respectively). Additional randomized trials are needed to replicate and extend these findings.

Other Musculoskeletal Pain

Reeves and Hassanein reported on a study of dextrose prolotherapy for anterior cruciate ligament (ACL) laxity. Of 16 evaluable patients, statistically significant improvements were found at six, 12, and 36 months in ACL laxity, pain, swelling, and knee range of motion. However, this was a small, nonrandomized trial and, as noted above, without placebo control, the extent that improvements with prolotherapy exceed those associated with a placebo cannot be determined.

A 2010 publication by Kim et al compared intra-articular prolotherapy with intra-articular corticosteroid injection for sacroiliac pain. The randomized double-blind study included 48 patients with sacroiliac joint pain lasting equal to or greater than three months, confirmed by equal to or greater than 50% improvement in response to local anesthetic block. The injections were performed on a biweekly schedule (maximum of three injections) under fluoroscopic guidance with confirmation of the intra-articular location with an arthrogram. Pain and disability scores were assessed at baseline, two weeks, and monthly after completion of treatment. At two weeks after treatment, all patients met the primary outcome measure of equal to or greater than 50% reduction in pain scores, and there was no significant difference between the two groups. The numerical rating scale 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 (ODI) 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 six months after treatment, 63.6% of patients in the prolotherapy group reported equal to or greater than 50% improvement from baseline in comparison with 27.2% of the steroid group. At 15 months after treatment, 58.7% of patients in the prolotherapy group reported relief equal to or greater than 50% in comparison 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.

Summary

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. The literature on prolotherapy consists of small randomized trials on a variety of pain syndromes, with inconsistent results. The body of scientific evidence does not permit conclusions concerning the effect of prolotherapy on health outcomes for chronic neck or back pain, tendinopathies of the upper or lower limbs, osteoarthritic pain, or other musculoskeletal pain conditions. Therefore, prolotherapy is considered investigational.

Practice Guidelines and Position Statements

The 2011 American College of Occupational and Environmental Medicine guideline on knee disorders states that prolotherapy is not recommended in the treatment of knee disorders.

U.S. Preventive Services Task Force Recommendations

Use of prolotherapy is not a preventive service.

Key Words:

Prolotherapy, Psyllium seed oil, sclerosing injections

Approved by Governing Bodies:

Not applicable

Benefit Application:

Coverage is subject to member's specific benefits. Group specific policy will supersede this policy when applicable.

ITS: Covered if covered by the Participating Home Plan

FEP contracts: FEP does not consider investigational if FDA approved and will be reviewed for medical necessity.

Current Coding:

HCPCS:

M0076 Prolotherapy

The M0076 is the correct code to use to report prolotherapy.

Providers should not bill for prolotherapy using the following codes:

CPT codes:

20550	Injection(s); tendon sheath, ligament, trigger points, or ganglion cyst
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, arthrography and/or anesthetic/steroid
64490-94495	Code range for injection(s), diagnostic or therapeutic agent, paravertebral facet (zygapophyseal) joint (or nerves innervating that joint)

References:

1. American College of Occupational and Environmental Medicine (ACOEM). Guideline: knee disorders. 2011; www.guideline.gov/content.aspx?id=36632&search=prolotherapy.
2. Best TM, Zhierska AE, Zeisig E, et al. A systematic review of four injection therapies for lateral epicondylitis: Prolotherapy, polidocanol, whole blood and platelet rich plasma. *Br J Sports Med*, July 2009; 43(7): 471-481.
3. Carayannopoulos A, Borg-Stein J, Sokolof J et al. Prolotherapy versus corticosteroid injections for the treatment of lateral epicondylitis: a randomized controlled trial. *PMR* 2011; 3(8):706-15.
4. Chakraverty R and Dias R. Audit of conservative management of chronic low back pain in a secondary care setting--part I: Facet joint and sacroiliac joint interventions. *Acupunct Med* 2004; 22(4):207-13.
5. Chou R, Atlas SJ, Stanos SP and Rosenquist RW. Nonsurgical interventional therapies for low back pain: A review of the evidence for an American Pain Society clinical practice guideline. *Spine*, May 2009; 34(10): 1078-1093.
6. Dagenais S, Yelland M, Del Mar C, and Schoene M. Prolotherapy injections for chronic low-back pain. *Cochrane Database Syst Review*, April 2007; (2): CD004059.
7. Dagenais S, Ogunseitan O, Haldeman S, et al. Side effects and adverse events related to intraligamentous injection of sclerosing solutions (prolotherapy) for back and neck pain: A survey of practitioners. *Arch Phys Med Rehabil*, July 2006; 87(7): 909-913.
8. Dagenais S, Haldeman S and Wooley JR. Intraligamentous injection of sclerosing solution (prolotherapy) for spinal pain: A critical review of the literature. *Spine J* 2005; 5(3):310-28.
9. Dagenais S, Mayer J, Haldeman S, et al. Evidence-informed management of chronic low back pain with prolotherapy. *Spine J* 2008; 8(1):203-12.
10. Hooper RA and Ding M. Retrospective case series on patients with chronic spinal pain treated with dextrose prolotherapy. *J Altern Complement Med* 2004; 10(4):670-4.
11. Kim WM, Lee HG, Jeong CW et al. A randomized controlled trial of intra-articular prolotherapy versus steroid injection for sacroiliac joint pain. *J Altern Complement Med* 2010; 16(12):1285-90.
12. Klein RG, Eek BC, DeLong WB et al. A randomized double-blind trial of dextrose-glycerine-phenol injections for chronic, low back pain, *J Spinal Disord* 1993; 6(1): 23-33.

13. Ongley MJ, Klein RG, Dorman TA et al. A new approach to the treatment of chronic low back pain, *Lancet* 1987; 2(8551): 143-6.
14. Rabago D, Best TM, Beamsley M, et al. A systematic review of prolotherapy for chronic musculoskeletal pain. *Clin J Sport Med* 2005; 15(5):376-80.
15. Rabago D, Best TM, Zgierska AE, et al. A systematic review of four injection therapies for lateral epicondylitis: prolotherapy, polidocanol, whole blood and platelet-rich plasma. *Br J Sports Med*. Jul 2009; 43(7):471-481.
16. Rabago D, Patterson JJ, Mundt M et al. Dextrose prolotherapy for knee osteoarthritis: a randomized controlled trial. *Ann Fam Med* 2013; 11(3):229-37.
17. Reeves KD, Hassanein K. Randomized prospective double-blind placebo-controlled study of dextrose prolotherapy for knee osteoarthritis with or without ACL laxity, *Altern Ther Health Med* 2000; 6(2): 68-74, 77-80.
18. Reeves KD, Hassanein K. Randomized, prospective, placebo-controlled double-blind study of dextrose prolotherapy for osteoarthritic thumb and finger (DIP, PIP, and trapeziometacarpal) joints: Evidence of clinical efficacy, *J Altern Complement Med* 2000; 6(4): 311-20.
19. Reeves KD, Hassanein KM. Long-term effects of dextrose prolotherapy for anterior cruciate ligament laxity, *Altern Ther Health Med* 2003; 9(3): 58-62.
20. Scarpone M, Rabago DP, Zgierska A, et al. The efficacy of prolotherapy for lateral epicondylitis: A pilot study. *Clin J Sport Med* 2008; 18(3):248-54.
21. Yelland MJ, Glasziou PP, Bogduk N et al. Prolotherapy injections, saline injections, and exercises for chronic low-back pain: A randomized trial, *Spine* 2004; 29(1): 9-16.
22. Yelland MJ, Mar C, Pirozzo S, et al. Prolotherapy injections for chronic low-back pain. *Cochrane Database Syst Rev* 2004; (2):CD004059.
23. Yelland MJ, Sweeting KR, et al. Prolotherapy injections and eccentric loading exercises for painful Achilles tendinosis: A randomised trial. *Br J Sports Med*, Apr 2011; 45(5):421-428.

Policy History:

Medical Policy Group, July 2005 (3)

Medical Policy Administration Committee, July 2005

Available for comment July 28-September 10, 2005

Medical Policy Group, June 2006 (1)

Medical Policy Group, June 2007 (1)

Medical Policy Group, February 2009 (4)

Medical Policy Group, February 2010 (1): Updated Description, Key Points and References

Medical Policy Panel, August 2010

Medical Policy Group, September 2010 (2)

Medical Policy Group August 2011 (3): Updated Key Points and References

Medical Policy Group, September 2012 (3): 2012 Update to Key Points and References

Medical Policy Panel, August 2013

Medical Policy Group, September 2013 (2): Updated with literature search through July 2013.

Policy statement unchanged. Key Points and References updated.

Medical Policy Panel, August 2014

Medical Policy Group, August 2014 (1): Update to Key Points and References, no change to policy statement

This medical policy is not an authorization, certification, explanation of benefits, or a contract. Eligibility and benefits are determined on a case-by-case basis according to the terms of the member's plan in effect as of the date services are rendered. All medical policies are based on (i) research of current medical literature and (ii) review of common medical practices in the treatment and diagnosis of disease as of the date hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment.

This policy is intended to be used for adjudication of claims (including pre-admission certification, pre-determinations, and pre-procedure review) in Blue Cross and Blue Shield's administration of plan contracts.