Prolotherapy

Policy

*Please see amendment for Pennsylvania Medicaid at the end of this CPB.*

Aetna considers prolotherapy (also known as proliferant therapy, proliferation therapy, joint sclerotherapy, or reconstructive ligament therapy) experimental and investigational for all indications, including the following (not an all-inclusive list), because there is inadequate evidence of its effectiveness:

- Achilles tendinosis
- Back pain
- Coccydynia
- Epicondylitis
- Hand osteoarthritis
- Iliotibial band syndrome
- Knee ligament instability
- Knee osteoarthritis
- Metatarso-phalangeal joint instability
- Myofascial pain
- Neuropathic pain
- Osgood-Schlatter disease
- Osteomyelitis pubis
- Plantar fasciopathy

Policy History

Last Review 02/09/2017
Effective: 03/16/1998
Next Review: 02/08/2018

Review History

Definitions

Additional Information

Clinical Policy Bulletin Notes
- Rotator cuff disease
- Sacroiliac joint pain
- Temporomandibular joint syndrome/Temporomandibular joint hypermobility
- Tendinopathies

Aetna considers prolozone therapy experimental and investigational for any diagnosis because there is no peer-reviewed published clinical literature regarding its effectiveness.

Aetna considers Sarapin, an herbal extract that has been used as a sclerosant in prolotherapy, experimental and investigational for all indications because there is inadequate evidence of its effectiveness.

**Note:** Ongley solution (also known as P2G) is a proliferant solution.

**Background**
Prolotherapy is a form of pain management that involves injecting a sclerosant solution into the region of joints, muscles or ligaments that are thought to cause chronic low back or joint pain. Prolotherapy, also known as reconstructive ligament therapy or joint sclerotherapy, may be used in an attempt to invoke the body's natural inflammatory response purportedly promoting new collagen growth to increase/improve joint stability or muscle regeneration/strengthening. Examples of injection solutions include, but may not be limited to, sodium morrhuate, dextrose (D50), glycerine, zinc sulfate, fibrin glue or platelet rich plasma (PRP) and often include an anesthetic agent, such as lidocaine.

The effectiveness of prolotherapy has not been verified by scientifically controlled studies. As early as 1978, the Medical Procedures Appropriateness Program of the Council of Medical Specialty Services (CMSS), based on input from the American Academy of Orthopedic Surgeons, the American Association of Neurological Surgeons, and the American College of Physicians,
concluded that prolotherapy had not been shown to be effective. Additionally, the Canadian Coordinating Office for Health Technology Assessment (2004) stated that "evidence from further controlled clinical trials of prolotherapy is clearly needed."

An assessment of prolotherapy prepared for the California Technology Assessment Forum (CTAF) concluded that prolotherapy does not meet CTAF's assessment criteria (Feldman, 2004). The assessment concluded "only one early study (Ongley et al, 1987) was able to demonstrate conclusively that prolotherapy was significantly superior to placebo for treatment of chronic low back pain. Subsequent research has not been able to replicate this finding. It is therefore not possible to conclude from the published literature that prolotherapy is superior to placebo injection for the treatment of chronic low back pain".

In the 1960s, Dr. Milne Ongley employed a more sclerosant than proliferative solution, as was common. Ongley searched the New Zealand Formulary and found an approved solution containing 50 % dextrose, 30 % glycerin, and 2.5 % phenol. It became known as "Ongley solution" or P2G. The study by Ongley et al (1987) was one of the few studies in the treatment of LBP to show a dramatic difference between treatment and placebo groups. There were several major drawbacks with the study by Ongley et al: (i) Subjects in the treatment group received an initial treatment of up to 60 ml lidocaine 0.5 % injection into the lumbosacral area compared with only 10 ml for the control group, (ii) The treatment group also received 50-mg triamcinolone injection into the gluteus medius compared with lidocaine 0.5 % injection for the control group, and (iii) the treatment group received actual spinal manipulation versus sham manipulation for the control group. The findings of the Ongley study were confounded by the use of combinational treatments (including spinal manipulation as well as triamcinolone injections); these findings need to be validated.
Ongley et al (1988) examined the effectiveness of prolotherapy for the treatment of ligament instability of knees. The study was conducted during a 9-month period in a private orthopedic office. A total of 30 patients presented with knee pain during the enrollment period, but 5 knees (in 4 patients) were selected because of substantial and reproducible ligament instability.

After informed consent had been given specific measurements were obtained. All measurements were taken by 1 researcher. The patients underwent multiple injections and were followed routinely. After 9 months repeated measurements were obtained. Subjective symptoms were recorded at entry and exit from the study. Ligament stability was measured by a commercially available computerized instrument that measures ligament function objectively and reliably in a complete 3-dimensional format. It consists of a chair equipped with a 6-component force platform and an electrogoniometer. With computer-integrated force and motion measurements, a standardized series of clinical laxity tests can be performed and an objective report obtained. Prior studies have compared clinical testing with objective tests and have established reproducibility. The proliferant solution is made up as follows: Dextrose 25% (694 mosmol/L), glycerine 25% (2,720 mosmol/L), phenol 2.5% (266 mosmol/L), and pyrogen-free water to 100%. At the time of injection it is diluted with an equal volume of 0.5% lidocaine. The proliferant injections are “peppered” into the lax ligament(s) usually at 2-weekly intervals, each offending ligament being treated an average of 4 times. A total of between 30 and 40 cc of the proliferant solution is injected into the appropriate portion of the joint ligaments. These researchers reported that their protocol was successful in reducing the laxity of unstable knees in this study group. All patients demonstrated improvement in measurable objective data. In addition, the subjective improvement and activity level was markedly improved. They noted that this study was one of the first to measure clinical outcome by the 3-dimensional computerized instrument. They believed this technique will help to evaluate intervention in unstable knees; and prolotherapy provided a well-tolerated new dimension in the treatment of ligamentous instability of the knee. It was
well-tolerated, as the preliminary results demonstrated.
Moreover, they stated that the drawbacks of this study were
the small number of subjects and the study design. They stated
that a randomized control without injection therapy and only
physiotherapy will be necessary to confirm these findings. The
authors believed, however, that these results were very
encouraging and provided the scientific format for further
research.

An UpToDate review on “Overview of the management of
overuse (chronic) tendinopathy” (Khan and Scott, 2014) lists
prolotherapy as one of the investigational therapies; it noted
that larger, randomized trials are needed to assess this
treatment before it can be recommended.

In a systematic review of prolotherapy for chronic
musculoskeletal pain, Rabago 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. Positive results compared with controls have
been reported in non-randomized and randomized controlled
trials (RCTs). Further investigation with high-quality RCTs with
non-injection control arms in studies specific to sport-related
and musculoskeletal conditions is necessary to determine the
effectiveness of prolotherapy.

Guidelines from the Work Loss Data Institute (2011) do not
recommend prolotherapy for various pain syndromes.

In a Cochrane review on prolotherapy injections for chronic LBP,
Degenais et al (2007) concluded that there is conflicting
evidence regarding the effectiveness of prolotherapy injections
for patients with chronic LBP. When used alone, prolotherapy is
not an effective treatment for chronic LBP. When combined
with spinal manipulation, exercise, and other co-interventions,
prolotherapy may improve chronic LBP and disability. These
researchers noted that conclusions are confounded by clinical
heterogeneity among studies and by the presence of co-
treatments.
Also, a practice guideline from the American Pain Society on low LBP (Chou et al, 2009) stated that prolotherapy is not recommended for persistent non-radicular LBP.

Furthermore, the clinical practice guideline on "Acute Low Back Problems in Adults" by the Agency for Health Care Policy and Research does not recommend ligamentous and sclerosant injections in the treatment of patients with acute low back pain (LBP). In a report, Yelland et al (2004) concluded that prolotherapy is no more effective than saline injections for the treatment of chronic LBP.

An UpToDate review on “Subacute and chronic low back pain: Nonsurgical interventional treatment” (Chou, 2014) states that “One systematic review included five trials of prolotherapy, compared with local anesthetic or saline injections, for chronic low back pain. There was no difference for short- or long-term pain or disability between prolotherapy and control intervention in three of the trials. Results from one trial that demonstrated short-term benefit for prolotherapy are difficult to interpret, because patients also received a number of co-interventions including forceful manipulation, injection of tender points, and exercise. A fifth trial was confounded by differences in the type of manipulation given to patients in the prolotherapy and control groups. Based on these trial results, a guideline from the American Pain Society recommends against prolotherapy for chronic low back pain”.

In addition, guidelines on low back pain from the American College of Occupational and Environmental Medicine (2007) have concluded that the use of prolotherapy for acute, subacute, chronic or radicular pain syndromes is not recommended.

Dagenais et al (2005) stated that results from clinical studies published to date indicate that prolotherapy may be effective at reducing spinal pain. Great variation was found in the injection and treatment protocols used in these studies that preclude definite conclusions. Future research should focus on those
solutions and protocols that are most commonly used in clinical practice and have been used in trials reporting effectiveness to help determine which patients, if any, are most likely to benefit from this treatment (Degenais et al, 2005).

Khan and colleagues (2008) presented the results of dextrose prolotherapy undertaken for chronic non-responding coccygodynia in 37 patients (14 men and 23 women, mean age of 36 years). Patients with chronic coccygodynia not responding to conservative treatment for more than 6 months were included; 27 of them had received local steroid injections. A visual analog score (VAS) was recorded for all patients before and after injection of 8 ml of 25 % dextrose and 2 ml of 2 % lignocaine into the coccyx. In 8 patients with a VAS of more than 4 after the second injection, a third injection was given 4 weeks later. The mean VAS before prolotherapy was 8.5. It was 3.4 after the first injection and 2.5 after the second injection. Minimal or no improvement was noted in 7 patients; the remaining 30 patients had good pain relief. The authors concluded that dextrose prolotherapy is an effective treatment option in patients with chronic, recalcitrant coccygodynia and should be used before undergoing coccygeotomy. They stated that randomized studies are needed to compare prolotherapy with local steroid injections or coccygeotomies.

In a pilot study, Scarpone et al (2008) examined the effectiveness of prolotherapy in the treatment of lateral epicondylitis. Subjects received injections of a solution made from 1 part 5 % sodium morrhuate, 1.5 parts 50 % dextrose, 0.5 parts 4 % lidocaine, 0.5 parts 0.5 % sensorcaine and 3.5 parts normal saline. Controls received injections of 0.9 % saline. Three 0.5-ml injections were made at the supracondylar ridge, lateral epicondyle, and annular ligament at baseline and at 4 and 8 weeks. The primary outcome was resting elbow pain (0 to 10 Likert scale). Secondary outcomes were extension and grip strength. Each was performed at baseline and at 8 and 16 weeks. One-year follow-up included pain assessment and effect of pain on activities of daily living. The groups were similar at baseline. Compared to controls,
Prolotherapy-treated subjects reported improved pain scores (4.5 +/- 1.7, 3.6 +/- 1.2, and 3.5 +/- 1.5 versus 5.1 +/- 0.8, 3.3 +/- 0.9, and 0.5 +/- 0.4 at baseline and at 8 and 16 weeks, respectively). At 16 weeks, these differences were significant compared to baseline scores within and among groups (p < 0.001). Prolotherapy subjects also reported improved extension strength compared to controls (p < 0.01) and improved grip strength compared to baseline (p < 0.05). Clinical improvement in prolotherapy-treated subjects was maintained at 52 weeks. There were no adverse events. The authors concluded that prolotherapy with dextrose and sodium morrhuate was well-tolerated, effectively decreased elbow pain, and improved strength testing in subjects with refractory lateral epicondylitis compared to control group injections. The findings of this pilot study (with a small sample size) need to be validated by more research.

In a systematic review on injection therapies for lateral epicondylitis (LE), Rabago and colleagues (2009) stated that there is strong pilot-level evidence supporting the use of prolotherapy in the treatment of LE. Moreover, they noted that rigorous studies of sufficient sample size, assessing these injection therapies using validated clinical, radiological and biomechanical measures, and tissue injury/healing-responsive biomarkers, are needed to determine the long-term effectiveness and safety, and whether these techniques can play a definitive role in the management of LE and other tendinopathies.

In a systematic review and meta-analysis, Krogh et al (2013) evaluated the comparative effectiveness and safety of injection therapies in patients with lateral epicondylitis. Randomized controlled trials comparing different injection therapies for lateral epicondylitis were included provided they contained data for change in pain intensity (primary outcome). Trials were assessed using the Cochrane risk of bias tool. Network (random effects) meta-analysis was applied to combine direct and indirect evidence within and across trial data using the final end point reported in the trials, and results for the arm-based
network analyses are reported as standardized mean differences (SMDs). A total of 17 trials (1,381 participants; 3 [18%] at low-risk of bias) assessing injection with 8 different treatments -- glucocorticoid (10 trials), botulinum toxin (4 trials), autologous blood (3 trials), platelet-rich plasma (2 trials), and polidocanol, glycosaminoglycan, prolotherapy, and hyaluronic acid (1 trial each) -- were included. Pooled results (SMD [95% confidence interval (CI)]) showed that beyond 8 weeks, glucocorticoid injection was no more effective than placebo (-0.04 [-0.45 to 0.35]), but only 1 trial (which did not include a placebo arm) was at low-risk of bias. Although botulinum toxin showed marginal benefit (-0.50 [-0.91 to -0.08]), it caused temporary paresis of finger extension, and all trials were at high-risk of bias. Both autologous blood (-1.43 [-2.15 to -0.71]) and platelet-rich plasma (-1.13 [-1.77 to -0.49]) were also statistically superior to placebo, but only 1 trial was at low-risk of bias. Prolotherapy (-2.71 [-4.60 to -0.82]) and hyaluronic acid (-5.58 [-6.35 to -4.82]) were both more efficacious than placebo, whereas polidocanol (0.39 [-0.42 to 1.20]) and glycosaminoglycan (-0.32 [-1.02 to 0.38]) showed no effect compared with placebo. The criteria for low-risk of bias were only met by the prolotherapy and polidocanol trials. The authors concluded that this systematic review and network meta-analysis of RCTs found a paucity of evidence from unbiased trials on which to base treatment recommendations regarding injection therapies for lateral epicondylitis.

In a pilot study, Rabago et al (2013) evaluated the effectiveness of 2 prolotherapy (PrT) solutions for chronic lateral epicondylitis. This study was a 3-arm RCT. A total of 26 adults (32 elbows) with chronic lateral epicondylitis for 3 months 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 weeks (all groups) and at 32 weeks (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 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-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 weeks (p < 0.05). There were no differences in magnetic resonance imaging scores. Satisfaction was high; there were no adverse events. The authors concluded that 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. They stated that the findings of this pilot study suggested the need for a definitive trial.

An UpToDate review on “Epicondylitis (tennis and golf elbow)” (Jayanthi, 2014) states that “The role of prolotherapy in the treatment of epicondylitis warrants further investigation”.

Sims et al (2014) stated that non-surgical approaches to treatment of lateral epicondylitis are numerous. These investigators examined RCTs of these treatments. Numerous databases were systematically searched from earliest records to February 2013. Search terms included "lateral epicondylitis", "lateral elbow pain", "tennis elbow", "lateral epicondylalgia", and "elbow tendinopathy" combined with "randomized controlled trial". Two reviewers examined the literature for eligibility via article abstract and full text. A total of 58 articles met eligibility criteria: (i) a target population of patients with symptoms of lateral epicondylitis; (ii) evaluation of treatment of lateral epicondylitis with the following non-surgical techniques: corticosteroid injection, injection technique, iontophoresis, botulinum toxin A injection, prolotherapy, platelet-rich plasma or autologous blood injection, bracing, physical therapy, shockwave therapy, or laser therapy; and (iii) a randomized
controlled trial design. Lateral epicondylitis is a condition that is usually self-limited. There may be a short-term pain relief advantage found with the application of corticosteroids, but no demonstrable long-term pain relief. Injection of botulinum toxin A and prolotherapy are superior to placebo but not to corticosteroids, and botulinum toxin A is likely to produce concomitant extensor weakness. Platelet-rich plasma or autologous blood injections have been found to be both more and less effective than corticosteroid injections. Non-invasive treatment methods such as bracing, physical therapy, and extracorporeal shockwave therapy do not appear to provide definitive benefit regarding pain relief. Some studies of low-level laser therapy show superiority to placebo whereas others do not. The authors concluded that there are multiple RCTs for non-surgical management of lateral epicondylitis, but the existing literature does not provide conclusive evidence that there is one preferred method of non-surgical treatment for this condition. Moreover, they stated that lateral epicondylitis is a condition that is usually self-limited, resolving over a 12- to 18-month period without treatment.

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."

The VATAP assessment also noted that the existing evidence base for prolotherapy shows wide variation in patient selection
criteria (Adams, 2008). The review noted that, in case series, findings from physical examination by a prolotherapist are part of the inclusion criteria, whereas all entry criteria from randomized controlled clinical trials were diagnosis-driven. The positive results seen in these case series may, in part, reflect careful selection criteria that a prolotherapist would employ in clinical practice using both diagnostic and examination findings.

The VATAP assessment stated that greater attention needs to be paid to using an appropriate control group (Adams, 2008). The report found that RCTs to date have employed control therapies with injection, which may invoke a response irrespective of injectant used, resulting in similar clinical improvement observed across study arms, while other RCTs have used control groups with very different treatment regimens such that it is not possible to attribute improvement in outcomes to prolotherapy alone.

The VATAP found that prolotherapy appears to have a safety profile comparable to that of other needling procedures, when performed by a skilled prolotherapist, but treatment protocols varied considerably across studies (Adams, 2008). The VATAP notes that, up to now, education and training for prolotherapists have relied on continuing education programs and mentoring and have not been standardized.

The VATAP report stated that prolotherapy along with conservative interventions (e.g., physiotherapy) appears to offer some pain relief when administered by a skilled prolotherapist in patients with LBP who are refractory to other treatments, but its independent role in these patients remains to be determined (Adams, 2008). The report stated that, given the increasing interest in this intervention, additional research and monitoring are warranted to clarify the safety profile and to determine the optimal proliferant, dosage and schedule, appropriate patient selection criteria, and the independent role of prolotherapy for a number of indications for which there are limited nonsurgical options for persons seeking chronic pain relief. The report stated that ongoing clinical trials of
prolotherapy should help define its clinical use.

Guidelines on chronic pain from the American College of Occupational and Environmental Medicine (2008) have concluded that the use of prolotherapy for neuropathic or myofascial pain is not recommended. American College of Occupational and Environmental Medicine (2011) guidelines on hand, wrist, and forearm disorders were unable to make a recommendation about the use of prolotherapy because of insufficient evidence.

In a prospective RCT, Kim and colleagues (2010) evaluated the efficacy and long-term effectiveness of intra-articular prolotherapy in relieving sacroiliac joint pain, compared with intra-articular steroid injection. The study included patients with sacroiliac joint pain, confirmed by greater than or equal to 50% improvement in response to local anesthetic block, lasting 3 months or longer, and who failed medical treatment. The treatment involved intra-articular dextrose water prolotherapy or triamcinolone acetonide injection using fluoroscopic guidance, with a bi-weekly schedule and maximum of 3 injections. Pain and disability scores were assessed at baseline, 2 weeks, and monthly after completion of treatment. The numbers of recruited patients were 23 and 25 for the prolotherapy and steroid groups, respectively. The pain and disability scores were significantly improved from baseline in both groups at the 2-week follow-up, with no significant difference between them. The cumulative incidence of greater than or equal to 50% pain relief at 15 months was 58.7% (95% CI: 37.9% to 79.5%) in the prolotherapy group and 10.2% (95% CI: 6.7% to 27.1%) in the steroid group, as determined by Kaplan-Meier analysis; there was a statistically significant difference between the groups (log-rank p < 0.005). The authors concluded that intra-articular prolotherapy provided significant relief of sacroiliac joint pain, and its effects lasted longer than those of steroid injections. They stated that further studies are needed to confirm the safety of the procedure and to validate an appropriate injection protocol.
Choi et al (2011) examined the most current evidence for treatment options in athletes with osteitis pubis and osteomyelitis pubis, attempting to determine which options provide optimal pain relief with rapid return to sport and prevention of symptom reoccurrence. Three databases -- MEDLINE, Cochrane Database of Systematic Reviews and CINAHL -- were searched using the OVID interface for all years between 1985 and May 2008. References were analysed from included studies, and additional relevant articles were obtained for inclusion. Inclusion criteria included (i) humans only, (ii) subjects had no apparent risk factors for development of osteitis pubis or osteomyelitis of the pubic symphysis other than athletic involvement, (iii) both physical examination findings and diagnostic imaging were used to confirm either diagnosis, and (iv) a definitive treatment strategy was identifiable for management of osteitis pubis or osteomyelitis of the pubic symphysis. In total, 25 articles were included in the review. There were no RCTs identified with this study's search strategy. A total of 195 athletes were diagnosed as having osteitis pubis (186 males, 9 females) and treated with either conservative measures/physical therapy, local injection with corticosteroids and/or local anesthetic, dextrose prolotherapy, surgery or antibiotic therapy. Six case reports/series described conservative treatment measures (physical therapy, rest, non-steroid anti-inflammatory drugs). Four case series explored the use of corticosteroid injections in treatment. One case series described the use of dextrose prolotherapy as a treatment modality. Six case series described various surgical techniques (pubic symphysis curettage, polypropylene mesh placement and pubic bone stabilisation) in treatment. Ten case reports/series (10 subjects) outlined antibiotic treatment of osteomyelitis of the pubic symphysis. The authors concluded that current medical literature shows only level 4 evidence of the treatment for osteitis pubis in 24 case reports/series in athletes. Without any direct comparison of treatment modalities, it is difficult to determine which individual treatment option is the most efficacious. They stated that further study comparing the different treatment options is needed to determine which modality provides the fastest
In a prospective, randomized, double-blind, placebo-controlled clinical study, Rafai et al (2011) evaluated the effectiveness of dextrose prolotherapy for the treatment of temporomandibular joint (TMJ) hypermobility. A total of 12 patients with painful subluxation or dislocation of the TMJ were randomly assigned to 1 of 2 equal-sized groups. Patients in the active group received 4 injections of dextrose solution (2 ml of 10 % dextrose and 1 ml of 2 % mepivacaine) for each TMJ, each 6 weeks apart, whereas patients in the placebo group received injections of placebo solution (2 ml of saline solution and 1 ml of 2 % mepivacaine) on the same schedule. A verbal scale expressing TMJ pain on palpation, maximal mouth opening (MMO), clicking sound, and frequency of luxations (number of locking episodes per month) were assessed at each injection appointment just before the injection procedure and 3 months after the last injection. The collected data were then statistically analyzed. By the end of the study, each group showed significant improvement in TMJ pain on palpation and number of locking episodes and insignificant improvement in clicking sound. With the exception of the MMO, there were no statistically significant differences throughout the study intervals between the active and placebo groups. The active group showed a significant reduction in MMO at the 12th week post-operatively. Differences compared with mean baseline value remained significant at the end of the follow-up period. On the other hand, the placebo group showed an insignificant difference in MMO throughout the study periods. For the last 2 intervals, the placebo group showed statistically significantly higher mean MMO values than the active group. By the end of the 12th post-operative week, the percentages of decrease in MMO were significantly greater in the active group. The authors concluded that prolotherapy with 10 % dextrose appears promising for the treatment of symptomatic TMJ hypermobility, as evidenced by the therapeutic benefits, simplicity, safety, patients’ acceptance of the injection technique, and lack of significant side effects. However, these investigators stated that continued research into prolotherapy's return to sport.
effectiveness in patient populations with large sample sizes and long-term follow-up is needed.

In a prospective, uncontrolled study with 1-year follow-up, Rabago et al (2012) examined if prolotherapy would improve pain, stiffness, and function in adults with symptomatic knee osteoarthritis (KOA) compared to baseline status. Adults with at least 3 months of symptomatic KOA, recruited from clinical and community settings, participated in the study. Participants received extra-articular injections of 15% dextrose and intra-articular prolotherapy injections of 25% dextrose at 1, 5, and 9 weeks, with as-needed treatments at weeks 13 and 17. Primary outcome measure was the validated Western Ontario McMaster University Osteoarthritis Index (WOMAC). Secondary outcome measure was the validated Knee Pain Scale (KPS). Tertiary outcome measure was procedure-related pain severity and participant satisfaction. A total of 36 participants (60 +/- 8.7 years old, 21 females) with moderate-to-severe KOA received an average of 4.3 +/- 0.7 prolotherapy injection sessions over a 17-week treatment period and reported progressively improved scores during the 52-week study on WOMAC and KPS measures. Participants reported overall WOMAC score improvement 4 weeks after the first injection session (7.6 +/- 2.4 points, 17.2%), and continued to improve through the 52-week follow-up (15.9 +/- 2.5 points, p < 0.001, 36.1%). Knee Pain Scale scores improved in both injected (p < 0.001) and un-injected knees (p < 0.05). Prescribed low-dose opioid analgesia effectively treated procedure-related pain. Satisfaction was high and there were no adverse events. Female gender, age of 46 to 65 years old, and body-mass index of 25 kg/m(2) or less were associated with greater improvement on the WOMAC instrument. The authors concluded that in adults with moderate-to-severe KOA, dextrose prolotherapy may result in safe, significant, sustained improvement of knee pain, function, and stiffness scores. Moreover, they stated that randomized multi-disciplinary effectiveness trials including evaluation of potential disease modification are needed to further evaluate the effectiveness of prolotherapy for KOA.
Gross et al (2013) stated that although there has been a recent increase in interest regarding injectable therapy for non-insertional Achilles tendinosis, there are currently no clear treatment guidelines for managing patients with this condition. These investigators conducted a systematic review of clinical outcomes following injectable therapy of non-insertional Achilles tendinosis, identified patient-specific factors that are prognostic of treatment outcomes, provided treatment recommendations based on the best available literature, and identified knowledge deficits that require further investigation. They searched Medline (1948 to March week 1 2012) and EMBASE (1980 to 2012 week 9) for clinical studies evaluating the effectiveness of injectable therapies for non-insertional Achilles tendinosis. Specifically, they included RCTs and cohort studies with a comparative control group. Data abstraction was performed by 2 independent reviewers. The Oxford Level of Evidence Guidelines and GRADE recommendations were used to rate the quality of evidence and to make treatment recommendations. A total of 9 studies fit the inclusion criteria for the review, constituting 312 Achilles tendons at final follow-up. The interventions of interest included platelet-rich plasma (n = 54), autologous blood injection (n = 40), sclerosing agents (n = 72), protease inhibitors (n = 26), hemodialysate (n = 60), corticosteroids (n = 52), and prolotherapy (n = 20). Only 1 study met the criteria for a high-quality RCT. All of the studies were designated as having a low quality of evidence. While some studies showed statistically significant effects of the treatment modalities, often studies revealed that certain injectables were no better than a placebo. The authors concluded that the literature surrounding injectable treatments for non-insertional Achilles tendinosis has variable results with conflicting methodologies and inconclusive evidence concerning indications for treatment and the mechanism of their effects on chronically degenerated tendons. They stated that prospective, randomized studies are needed in the future to guide Achilles tendinosis treatment recommendations using injectable therapies.

An UpToDate review on “Iliotibial band syndrome” (Jackson,
2014) states that “Prolotherapy is the injection of irritants into or adjacent to tendons with the goal of inciting a healing response. This technique has not been the subject of controlled studies in ITBS”.

According to Martindale's Extrapharmacopoeia, Sarapin is a brand name for an extract of the pitcher plant, or Sarracenia Purpurea. Martindale's notes that "the roots and leaves of Sarracenia Purpurea have been used in the form of an aqueous distillate, administered by local injection, for neuromuscular or neuralgic pain."

Sarapin is typically administered in conjunction with prolotherapy. There is inadequate evidence of the effectiveness of Sarapin for pain. One clinical study involving 180 patients found greater pain relief in patients administered facet blocks with Sarapin than those without (Manchikanti et al, 2000). Another study, using an animal model, found Sarapin to have no anesthetic effect (Harkins et al, 1997). Other studies found no effect of the addition of Sarapin on neural blockade (Manchikanti et al, 2004; Manchikanti et al, 2006; Manchikanti et al, 2007). Levin (2009) stated that injection of corticosteroid or Sarapin on the lumbar medial branch nerves is ineffective for the treatment of acute/subacute lumbo-sacral radicular pain.

Prolozone therapy is an injection technique similar to prolotherapy that uses ozone. According to the practitioners using this technique, the use of ozone causes the joint to heal much more quickly than in traditional prolotherapy because ozone is a highly reactive molecule and when injected into a joint capsule it is able to stimulate the fibroblastic joint repairing abilities.

Metatarso-Phalangeal Joint Instability:

Ojofeitimi et al (2016) noted that professional ballet and modern dancers spend an inordinate amount of time on demi pointe (rising onto their forefeet), placing excessive force on the metatarso-phalangeal (MP) joints and putting them at risk of
Surgical treatment of this condition is well-described in the literature. However, studies describing conservative management particularly in dance populations, are lacking. These investigators presented the case of a 33-year old dancer with insidious onset of medial arch and 2nd and 3rd MP joint pain. Functional deficits included the inability to walk barefoot, perform demi releve, or balance in demi pointe. Imaging studies revealed OA of the 1st MP joint, 2nd MP joint calcification, capsulitis, and plantar plate rupture leading to a diagnosis of instability. The dancer underwent a treatment program that included taping, padding, physical therapy, a series of prolotherapy injections, and activity modification. The dancer was seen for a total of 37 physical therapy sessions over the 16-week rehabilitation period. At the time of discharge, the patient had returned to full duty and performed all choreography with taping and padding. Repeated single leg jumps and turns on the right foot, however, still caused discomfort. At her 6 month follow-up, the dancer’s total Dance Functional Outcome Score had improved from 11 % to 90 % and her and Short Form 36 (SF-36) physical scores improved from 24 to 47. One year after discharge, the dancer reported pain-free dancing with no taping or padding. The authors concluded that this case report described early diagnosis and a multi-modal treatment approach in a professional dancer with significant disability secondary to MTP joint instability. (Level of Evidence Therapy: Level 4). This was a single-case study with short-term follow-up (6 months); its finding were confounded by the multi-modality approach. Thus, the role of prolotherapy in the treatment of MP joint instability has to be determined by well-designed studies.

_Osgood-Schlatter Disease and Plantar Fasciopathy:_

In a systematic review, Sanderson and Bryant (2015) evaluated existing research to determine the safety and effectiveness of prolotherapy injections for treatment of lower limb tendinopathy and fasciopathy. Nine databases were searched (Medline, Science Direct, AMED, Australian Medical Index, APAIS-Health, ATSIhealth, EMBASE, Web of Science, OneSearch)
without language, publication or data restrictions for all relevant articles between January 1960 and September 2014. All prospective randomized and non-randomized trials, cohort studies, case-series, cross-sectional studies and controlled trials assessing the effectiveness of one or more prolotherapy injections for tendinopathy or fasciopathy at or below the superior aspect of the tibia/fibula were included. Methodological quality of studies was determined using a modified evaluation tool developed by the Cochrane Musculoskeletal Injuries Group. Data analysis was performed to determine the mean change of outcome measure scores from baseline to final follow-up for trials with no comparative group, and for RCTs, standardized mean differences between intervention groups were calculated. Pooled SMD data were calculated where possible to determine the statistical heterogeneity and overall effect for short-, intermediate- and long-term data; adverse events (AEs) were also reported. A total of 203 studies were identified, 8 of which met the inclusion criteria. These were then grouped according to tendinopathy or fasciopathy being treated with prolotherapy injections: Achilles tendinopathy, plantar fasciopathy and Osgood-Schlatter disease. The methodological quality of the 8 included studies was generally poor, particularly in regards to allocation concealment, intention-to-treat analysis and blinding procedures. Results of the analysis provided limited support for the hypothesis that prolotherapy is effective in both reducing pain and improving function for lower limb tendinopathy and fasciopathy, with no study reporting a mean negative or non-significant outcome following prolotherapy injection. The analysis also suggested prolotherapy injections provided equal or superior short-, intermediate- and long-term results to alternative treatment modalities, including eccentric loading exercises for Achilles tendinopathy, platelet-rich plasma for plantar fasciopathy and usual care or lignocaine injections for Osgood-Schlatter disease. No AEs following prolotherapy injections were reported in any study in this review. The authors stated that the conclusions of this review were derived from the best available scientific evidence. It was intended that the results of this study would assist clinical decision-making by
practitioners. These investigators stated that the results of this review found limited evidence that prolotherapy injections are a safe and effective treatment for Achilles tendinopathy, plantar fasciopathy and Osgood-Schlatter disease, however more robust research using large, methodologically-sound RCTs is needed to substantiate these findings.

**Rotator Cuff Disease:**

In a retrospective, case-control study, Lee and colleagues (2015) examined the effectiveness of prolotherapy for refractory rotator cuff disease. Patients with non-traumatic refractory rotator cuff disease \( n = 151 \) who were unresponsive to 3 months of aggressive conservative treatment. Of the patients, 63 received prolotherapies with 16.5 % dextrose 10-ml solution (treatment group), and 63 continued conservative treatment (control group). Main outcome measures included VAS score of the average shoulder pain level for the past 1 week, Shoulder Pain and Disability Index (SPADI) score, isometric strength of the shoulder abductor, active range of motion (AROM) of the shoulder, maximal tear size on ultrasonography, and number of analgesic ingestions per day. Over 1-year follow-up, 57 patients in the treatment group and 53 in the control group were analyzed. There was no significant difference between the 2 groups in age, sex, shoulder dominance, duration of symptoms, and ultrasonographic findings at pre-treatment. The average number of injections in the treatment group was 4.8 ± 1.3. Compared with the control group, VAS score, SPADI score, isometric strength of shoulder abductor, and shoulder AROM of flexion, abduction, and external rotation showed significant improvement in the treatment group; there were no AEs. The authors concluded that this was the first study to evaluate the effectiveness of prolotherapy in rotator cuff disease. Prolotherapy showed improvement in pain, disability, isometric strength, and shoulder AROM in patients with refractory chronic rotator cuff disease. The authors concluded that the results suggested positive outcomes, but caution is needed in directly interpreting it as an effective treatment option, considering the limitations of this non-randomized
retrospective study. They stated that to show the effectiveness of prolotherapy, further studies on prospective RCTs are needed.

Vanden Bossche and Vanderstraeten (2015) described the protocol of a phase III clinical trial evaluated functional, clinical, and subjective parameters in patients with rotator cuff syndrome and bursitis treated with Traumeel injections versus corticosteroid injections and versus placebo. This is a multi-center, randomized, double-blind, 16-week, 3-arm, parallel-group, active- and placebo-controlled trial to assess the safety and effectiveness of Traumeel 2-ml injection versus dexamethasone 8-mg injection versus placebo (saline solution). Patients will be randomly allocated to Traumeel, dexamethasone or placebo in a 2:2:1 randomization. After 1 week screening, patients will receive 3 injections at weekly intervals (days 1, 8 and 15) with additional follow-up assessments on day 22, a telephone consultation in week 9 and a final visit at week 15. Male and female patients aged 40 to 65 years, inclusive, will be recruited if they have acute episodes of chronic rotator cuff syndrome and/or bursitis. Patients with calcifications in the shoulder joint or a complete rotator cuff tear will be excluded. At least 160 patients will be recruited. All subacromial injections will be performed under ultrasound guidance utilizing a common technique. The only rescue medication permitted will be paracetamol (acetaminophen), with usage recorded. The primary end-point is change from baseline in abduction-rotation pain VAS (0 to 100 mm scale, 0 corresponds to no pain and 100 to extreme pain) at day 22 (Traumeel injections versus dexamethasone injections) for active external rotation. Secondary effectiveness parameters include ROM, disability of arm, shoulder, hand score and patient's/investigator's global assessment. Clinical effectiveness will be evaluated as non-inferiority of Traumeel with respect to dexamethasone regarding the primary effectiveness parameter. The authors stated that it is hoped that the results of this trial will expand the treatment options and evidence base available for the management of rotator cuff disease.
Hand and Knee Osteoarthritis:

Sit and associates (2016) stated that prolotherapy is an emerging treatment for symptomatic knee OA but its effectiveness is uncertain. These investigators conducted a systematic review with meta-analysis to synthesize clinical evidence on the effect of prolotherapy for knee OA. A total of 15 electronic databases were searched from their inception to September 2015. The primary outcome of interest was score change on the WOMAC; 3 RCTs of moderate risk of bias and 1 quasi-randomized trial were included, with data from a total of 258 patients. In the meta-analysis of 2 eligible studies, prolotherapy was superior to exercise alone by a SMD of 0.81 (95% CI: 0.18 to 1.45, p = 0.012), 0.78 (95% CI: 0.25 to 1.30, p = 0.001) and 0.62 (95% CI: 0.04 to 1.20, p = 0.035) on the WOMAC composite scale; and WOMAC function and pain subscale scores, respectively. Moderate heterogeneity exists in all cases. The authors concluded that prolotherapy conferred a positive and significant beneficial effect in the treatment of knee OA; adequately powered, longer-term trials with uniform end-points are needed to better elucidate the effectiveness of prolotherapy.

In a systematic review and meta-analysis, Hung and colleagues (2016) compared the effectiveness of dextrose prolotherapy versus control injections and exercise in the management of OA pain. PubMed and Scopus were searched from the earliest record until February 2016. One single-arm study and 5 RCTs were included, comprising 326 participants. These investigators estimated the effect sizes of pain reduction before and after serial dextrose injections and compared the values between dextrose prolotherapy, comparative regimens, and exercise 6 months after the initial injection. Regarding the treatment arm using dextrose prolotherapy, the effect sizes compared with baseline were 0.65 (95% CI: 0.14 to 1.17), 0.84 (95% CI: 0.40 to 1.27), 0.85 (95% CI: 0.60 to 1.10), and 0.87 (95% CI: 0.53 to 1.21) after the 1st, 2nd, 3rd, and 4rth or more injections, respectively. The overall effect of dextrose was better than control injections (effect size, 0.36; 95% CI: 0.10 to 0.63).
Dextrose prolotherapy had a superior effect compared with local anesthesia (effect size, 0.38; 95 % CI: 0.07 to 0.70) and exercise (effect size, 0.71; 95 % CI: 0.30 to 1.11). There was an insignificant advantage of dextrose over corticosteroids (effect size, 0.31; 95 % CI: -0.18 to 0.80) which was only estimated from 1 study. The authors concluded that dextrose injections decreased pain in OA patients; but did not exhibit a positive dose-response relationship following serial injections. Dextrose prolotherapy was found to provide a better therapeutic effect than exercise, local anesthetics, and probably corticosteroids when patients were re-tested 6 months following the initial injection. They also noted that The effect of prolotherapy did not differ between hand and knee osteoarthritis.

This study had several drawbacks: (i) the number of trials eligible for meta-analysis was limited, and heterogeneity existed in the patient populations, injection protocols, comparative regimens, and outcome assessment, (ii) these researchers did not analyze effect sizes of functional improvements because the data were not available in each retrieved trial. (iii) although previous research proposed that the benefit of dextrose prolotherapy derived from its chondro-protective effect or modulation of intra-articular cytokines, these theories could not be proved by this meta-analysis since there were few data about the measurement of cartilage thickness and intra-articular cytokine level in the retrieved articles, (iv) hyaluronic acid and platelet-rich plasma are known to counteract OA. Although dextrose prolotherapy appeared to be more effective than the use of corticosteroids and local anesthetics, the comparison with commonly used regimens like hyaluronic acid or platelet-rich plasma was lacking in this literature search. This subject should be investigated in future prospective studies, (v) the treatment responsiveness using binary data, which considered the standard outcome variable in pain medicine, is not reported in the included studies. Therefore, these investigators used the effect sizes retrieved from continuous variables like changes in pain or function instead in the quantitative analysis, and (vi) the interpretation of the effect of dextrose compared with corticosteroids should
be cautious because the finding was derived from only a single study.

**Temporomandibular Joint Hypermobility:**

Comert Kilic and Gungormus (2016) performed a randomized clinical trial involving adult patients with bilateral TMJ hypermobility referred for treatment. The sample comprised 30 consecutive patients, who were divided randomly into 2 groups. The TMJ hypermobility was treated with either saline (placebo group) or dextrose injections (study group). The solution was injected into 5 different TMJ areas in 3 sessions at monthly intervals. The predictor variable was the treatment technique. The outcome variables were VAS evaluations and maximum inter-incisal opening (MIO). Outcome variables were recorded pre-operatively and at 12 months post-operatively. Descriptive and bivariate statistics were computed, and significance was set at a p-value of less than 0.05. The follow-up sample comprised 26 subjects: 12 in the placebo group and 14 in the study group. Masticatory efficiency increased and general pain complaints and joint sounds decreased significantly in both groups; MIO decreased significantly only in the study group. Insignificant changes in the other parameters were found for both groups. After estimating differences between follow-up and baseline outcomes, the mean change in primary outcome variables showed no statistically significant difference between the 2 groups. The authors concluded that these findings suggested that dextrose prolotherapy is no more effective than placebo treatment for any of the outcome variables of TMJ hypermobility assessed.

Reeves and colleagues (2016) stated that prolotherapy involves the injection of non-biologic solutions, typically at soft tissue attachments and within joint spaces, to reduce pain and improve function in painful musculoskeletal conditions. A variety of solutions have been used; dextrose prolotherapy is the most rigorously studied and is the focus of this review. Although the mechanism of action is not clearly known, it is
likely to be multifactorial. The authors concluded that data on effectiveness for temporomandibular dysfunction are promising but insufficient for recommendations; research on the mechanism of action and clinical effects of dextrose prolotherapy are under way.

CPT Codes / HCPCS Codes / ICD-10 Codes

Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by "+":

Other CPT codes related to the CPB:

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>20550</td>
<td>Injection(s); single tendon sheath, or ligament, aponeurosis (e.g., plantar &quot;fascia&quot;)</td>
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<tr>
<td>20600</td>
<td>Arthrocentesis, aspiration and/or injection</td>
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<td>20611</td>
<td></td>
</tr>
</tbody>
</table>

HCPCS codes not covered for indications listed in the CPB:

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>M0076</td>
<td>Prolotherapy [joint sclerotherapy and reconstructive ligament therapy]</td>
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</table>

ICD-10 codes not covered for indications listed in the CPB (not all-inclusive):

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
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<tbody>
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<td>M17.0</td>
<td>Osteoarthritis of knee</td>
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<tr>
<td>M17.9</td>
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<tr>
<td>M24.00</td>
<td>Other specific joint derangements</td>
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<tr>
<td>M24.176</td>
<td></td>
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<tr>
<td>M24.30</td>
<td></td>
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<tr>
<td>M24.9</td>
<td></td>
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<tr>
<td>M25.374</td>
<td>Other instability, foot [metatarso-phalangeal joint instability]</td>
</tr>
<tr>
<td>M25.376</td>
<td></td>
</tr>
<tr>
<td>M26.601</td>
<td>Temporomandibular joint disorders</td>
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<tr>
<td>M26.69</td>
<td></td>
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<tr>
<td>M53.3</td>
<td>Sacroccygeal disorders, not elsewhere classified [coccygodynia] [pain]</td>
</tr>
<tr>
<td>M54.5</td>
<td>Low back pain</td>
</tr>
<tr>
<td>Code</td>
<td>Description</td>
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<tr>
<td>--------------</td>
<td>----------------------------------------------------------</td>
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<tr>
<td>M67.90 - M67.99</td>
<td>Unspecified disorder of synovium and tendon</td>
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<tr>
<td>M72.2</td>
<td>Plantar fascial fibromatosis [plantar fasciopathy]</td>
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<tr>
<td>M75.100 - M75.122</td>
<td>Rotator cuff tear or rupture, not specified as traumatic</td>
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<td>M76.30 - M76.32</td>
<td>Iliotibial band syndrome</td>
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<td>Neuralgia and neuritis, unspecified</td>
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<td>M86.18, M86.68</td>
<td>Other acute or chronic osteomyelitis [osteomyelitis pubis]</td>
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<tr>
<td>M92.50 - M92.52</td>
<td>Juvenile osteochondrosis of tibia and fibula [Osgood-Schlatter disease]</td>
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<td>S03.00x+ - S03.02x+</td>
<td>Dislocation of jaw</td>
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<tr>
<td>S33.5xx+ - S33.9xx+</td>
<td>Sprain of lumbar/sacral spine/joint/ligament</td>
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<tr>
<td>S43.421+ - S43.429+</td>
<td>Sprain of rotator cuff capsule</td>
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<tr>
<td>S46.001+ - S46.099+</td>
<td>Injury of muscle(s) and tendon(s) of the rotator cuff of shoulder</td>
</tr>
</tbody>
</table>

The above policy is based on the following references:


30. Rabago D, Best TM, Zgierska AE, et al. A systematic review of four injection therapies for lateral epicondylitis:


42. American College of Occupational and Environmental Medicine (ACOEM). Hand, wrist, and forearm disorders


49. Khan K, Scott A. Overview of the management of overuse
(chronic) tendinopathy. UpToDate [serial online]. Waltham, MA: UpToDate; reviewed December 2014.


52. Jackson J. Iliotibial band syndrome. UpToDate [serial online]. Waltham, MA: UpToDate; reviewed December 2014.


AETNA BETTER HEALTH® OF PENNSYLVANIA

Amendment to
Aetna Clinical Policy Bulletin Number:
CPB 0207 Prolotherapy

There are no amendments for Medicaid.