Clinical Policy Title: Prolotherapy

Clinical Policy Number: 14.02.08

Effective Date: April 1, 2016
Initial Review Date: January 20, 2016
Most Recent Review Date: February 15, 2017
Next Review Date: February 2018

Policy contains:
- Musculoskeletal pain.
- Prolotherapy.
- Injection therapy.

Related policies:

CP# 00.02.06 Infusible pharmaceuticals for bone pain management
CP# 03.02.07 Spine pain — facet joint injection
CP# 03.03.05 Spine pain — trigger point injection
CP# 18.04.02 Hierarchy of chronic pain
CP# 00.02.08 Intra-articular hyaluronic acid injection for osteoarthritis

ABOUT THIS POLICY: Prestige Health Choice has developed clinical policies to assist with making coverage determinations. Prestige Health Choice’s clinical policies are based on guidelines from established industry sources, such as the Centers for Medicare & Medicaid Services (CMS), state regulatory agencies, the American Medical Association (AMA), medical specialty professional societies, and peer-reviewed professional literature. These clinical policies along with other sources, such as plan benefits and state and federal laws and regulatory requirements, including any state- or plan-specific definition of “medically necessary,” and the specific facts of the particular situation are considered by Prestige Health Choice when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state or federal laws and/or regulatory requirements, the plan benefits and/or state and federal laws and/or regulatory requirements shall control. Prestige Health Choice’s clinical policies are for informational purposes only and not intended as medical advice or to direct treatment. Physicians and other health care providers are solely responsible for the treatment decisions for their patients. Prestige Health Choice’s clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, Prestige Health Choice will update its clinical policies as necessary. Prestige Health Choice’s clinical policies are not guarantees of payment.

Coverage policy

Prestige Health Choice considers the use of prolotherapy for musculoskeletal conditions to be investigational and, therefore, not medically necessary.

Limitations:

Coverage determinations are subject to benefit limitations and exclusions as delineated by the state Medicaid authority. The Florida Medicaid website can be accessed at http://ahca.myflorida.com/Medicaid/.

All other uses of prolotherapy are not medically necessary.
Alternative covered services:

- Surgical treatment.
- Non-surgical approaches, including anti-inflammatory medications; physical or occupational therapy; immobilization; using heat or cold; reducing workload and increasing rest, relaxation, and biofeedback techniques; strengthening and conditioning exercises; stretching exercises; and therapeutic massage.

Background

Musculoskeletal conditions are among the most disabling and costly conditions suffered by Americans (BMUS, 2014). Musculoskeletal medical conditions were reported by 126.6 million adults in the United States, representing more than one in two persons at least 18 years of age. Musculoskeletal conditions are found among all age groups, with the proportion of persons reporting these conditions increasing with age. Musculoskeletal diagnoses accounted for 18 percent, or 223.6 million, of the 1.3 billion medical diagnoses, included in hospital discharge records, emergency department, outpatient clinic visits, and physician office visits in the United States in 2010 and 2011 (BMUS, 2014).

Causes of musculoskeletal pain include the wear and tear of daily activities or trauma to an area, postural strain, repetitive movements, overuse, and prolonged immobilization. Changes in posture or poor body mechanics may bring about spinal alignment problems and muscle shortening, causing other muscles to be misused and become painful.

Musculoskeletal pain is best treated by treating its cause. Non-surgical approaches include anti-inflammatory medications; physical or occupational therapy; immobilization; using heat or cold; reducing workload and increasing rest, relaxation, and biofeedback techniques; strengthening and conditioning exercises; stretching exercises; and therapeutic massage. Complementary therapies such as chiropractic care, acupuncture or acupressure may be used.

When conservative treatments fail to alleviate the pain, injection therapies in or around the painful sites may be used. Prolotherapy, also known as regenerative injection therapy, involves injecting an irritant into an injured joint, ligament, or tendon to relieve pain (AOAPRM, 2017). Used since the 1930s, prolotherapy (termed from proliferant therapy) has emerged as a treatment option for chronic musculoskeletal injuries. Its mechanism of action has not been clearly established but is hypothesized to stimulate growth factors in the inflammatory healing cascade and promote musculoskeletal repair by producing new collagen tissue.

Injection agents may include ingredients such as dextrose, morrhuate sodium, saline, sarapin, procaine, or lidocaine. In recent years, platelet-rich plasma (PRP) and autologous adult stem cell sources typically taken from bone marrow or adipose (fat) tissue have emerged. Prolotherapy techniques and injected solutions vary by condition, clinical severity, and practitioner preferences and commonly consist of
several injection sessions delivered every three to six weeks over several months (Rabago, 2010).

**Regulation:**

The Food and Drug Administration (FDA) has approved the most commonly used agents, such as dextrose and lidocaine, for injection, but these substances are not specifically approved for prolotherapy for joint and ligamentous injections, making such use off-label. Morrhuate sodium is not currently listed as an FDA-approved sclerosing agent (FDA, 2015).

**Searches**

Prestige Health Choice searched PubMed and the databases of:

- UK National Health Services Centre for Reviews and Dissemination.
- Agency for Healthcare Research and Quality’s National Guideline Clearinghouse and other evidence-based practice centers.
- The Centers for Medicare & Medicaid Services (CMS).

We conducted searches on January 6, 2017. Search term was "prolotherapy."

We included:

- **Systematic reviews**, which pool results from multiple studies to achieve larger sample sizes and greater precision of effect estimation than in smaller primary studies. Systematic reviews use predetermined transparent methods to minimize bias, effectively treating the review as a scientific endeavor, and are thus rated highest in evidence-grading hierarchies.
- **Guidelines based on systematic reviews**.
- **Economic analyses**, such as cost-effectiveness, and benefit or utility studies (but not simple cost studies), reporting both costs and outcomes — sometimes referred to as efficiency studies — which also rank near the top of evidence hierarchies.

**Findings**

Few professional guidelines address prolotherapy. A 2011 guideline on low back pain from the Institute for Health Economics (IHE) determined that prolotherapy was not recommended as a sole treatment, but could be used as an adjunctive therapy. The most commonly reported adverse events were temporary increases in back pain and stiffness following injections, and some patients had severe headaches suggestive of lumbar puncture, but no serious or permanent adverse events were reported (IHE, 2011).

Another guideline, by the American Pain Society in 2009, addressed reduction in low back and radicular pain. The guideline concluded there was fair to good evidence that prolotherapy, facet joint injection, intradiscal steroid injection, and percutaneous intradiscal radiofrequency thermocoagulation are not
effective (Chou, 2009). A panel of Canadian experts, after a review of 16 articles, found that prolotherapy may be more effective for relieving low back pain, tendinopathy, and osteoarthritis when compared with saline injections or exercise, or when compared with pre-prolotherapy pain levels (CADTH, 2014). Numerous other guidelines on pain relief do not address effectiveness of prolotherapy. Initial systematic reviews found no consistent evidence that prolotherapy injections reduced various types of pain. A review of four studies (n = 344) found that compared to control injections, two of four showed significant pain reductions in chronic low back pain (Yelland, 2004), which was the same finding of another systematic review of chronic musculoskeletal pain (Rabago, 2005). The former study assessed only pain, while the latter assessed pain, disability, range of motion, and patellofemoral cartilage thickness.

Subsequent reviews could not identify consistent evidence of the efficacy of prolotherapy. One review of 41 trials for pain reduction in lateral epicondylalgia, some of which involved prolotherapy, found the treatment superior to placebo, but inferior to sodium hyaluronate or botulinum toxin (Coombes, 2010). Another review of 58 trials found prolotherapy injections superior to placebo, but inferior to corticosteroids for long-term pain relief (Sims, 2014). A review of three trials (n = 206) found prolotherapy no more effective than control injections for chronic low-back pain and disability; but two other trials found greater effectiveness when prolotherapy and spinal manipulation and exercise were used (Dagenais, 2007).

The only systematic review prior to 2016 to find consistently superior results for prolotherapy included three controlled trials. Compared to saline, prolotherapy reduced pain in each study (90 vs. 22 percent, 66 vs. 11.5 percent, and 94 percent vs. baseline). Changes for all but the middle study were statistically significant (Rabago, 2009).

In 2016, several systematic reviews found greater evidence of prolotherapy’s effectiveness. One consisting of six trials (n = 326) comparing dextrose prolotherapy vs. control injections for osteoarthritis over six months found that prolotherapy reduced pain 64 and 62 percent compared to controls and local anesthesia; the greatest reductions occurred after first injection, but the gains lessened after each month’s injection thereafter (Hung, 2016). Another analysis of two trials (n=258) found dextrose prolotherapy reduced knee osteoarthritis problems by 19 – 22 percent (Sit, 2016). A third concluded that prolotherapy might be effective for lateral epicondylalgia, even though this conclusion needed more confirmation (Dong, 2016). A November 2016 Hayes review of 12 abstracts concluded that prolotherapy generated “conflicting findings” on reducing pain (Hayes, 2016).

Policy updates:

This version of the policy includes an additional four professional guideline/other references, plus an additional 11 peer reviewed references.

Summary of clinical evidence:
<table>
<thead>
<tr>
<th>Citation</th>
<th>Content, Methods, Recommendations</th>
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<tbody>
<tr>
<td>Sanderson (2015)</td>
<td><strong>Key points:</strong></td>
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</tbody>
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| Lower limb tendinopathy and fasciopathy | • Systematic review of three RCTs and five case series.  
  • Prolotherapy injections are safe and effective in reducing pain and improving function for Achilles tendinopathy, plantar fasciopathy, and Osgood-Schlatter disease.  
  • Prolotherapy provides equal or superior results to alternative treatment modalities, including eccentric loading exercises for Achilles tendinopathy, platelet-rich plasma for plantar fasciopathy and usual care or lidocaine injections for Osgood-Schlatter disease. |
| Canadian Agency for Drugs and Technologies in Health (CADTH, 2014) | **Key points:**                   |
| Musculoskeletal pain: low back pain (LBP); tendinopathy; knee osteoarthritis (OA) | • Analysis of one systematic review, seven RCTs, and eight case series using dextrose, dextrose-morrhuate, or morrhuate.  
  • Overall quality: low for RCTs and case series with high risk of bias. Small sample size, lack of validation of the clinical outcome measures.  
  • LBP (one RCT, seven case series): dextrose prolotherapy treatment of LBP might improve pain relief and last longer than corticosteroid treatment.  
  • Tendinopathy (one systematic review, three RCTs, two case series): dextrose prolotherapy might improve pain caused by tendinopathy, including lateral epicondylitis, Achilles tendinosis, and patellar tendinopathy.  
  • Knee OA (three RCTs, four case series): dextrose, dextrose-morrhuate, or morrhuate prolotherapy might improve pain and function. The benefit of dextrose prolotherapy for treatment of hand OA was unclear. |
| Sims (2014)                           | **Key points:**                   |
| Non-surgical treatment of lateral epicondylitis | • Systematic review of 58 articles, patients with symptoms of or who were treated for lateral epicondylitis.  
  • Prolotherapy and botulinum A injections superior to placebo, but not to corticosteroids.  
  • No consistent effectiveness found for platelet-rich plasma or autologous blood injections, physical therapy, or extracorporeal shock wave therapy. |
| Refai (2011)                          | **Key points:**                   |
| Temporomandibular joint (TMJ) hypermobility | • 12 patients were randomly assigned to either active group who received four injections of dextrose solution (2 mL of 10% dextrose and 1 mL of 2% mepivacaine) for each TMJ, each six weeks apart, or placebo group (2 mL of saline solution and 1 mL of 2% mepivacaine) on the same schedule. Outcomes were a verbal scale expressing TMJ pain on palpation, maximal mouth opening (MMO), clicking sound, and frequency of luxations (number of locking episodes per month) assessed at each injection appointment just before the injection procedure and three months after the last injection.  
  • 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, but no statistically significant between-group differences.  
  • The active group showed a significant reduction in MMO at the 12th week postoperatively. Differences compared with mean baseline value remained significant at the end of the follow-up period. The placebo group showed an insignificant improvement throughout the study periods. For the last two intervals, the placebo group showed statistically significantly higher mean MMO values than the active group. By the end of the 12th postoperative week, the percentages of decrease in MMO were significantly
greater in the active group.

- **Conclusion:** Prolotherapy with 10% dextrose appears promising for the treatment of symptomatic TMJ hypermobility, but more research with large sample sizes and long-term follow-up is needed.

### Choi (2011)

**Osteitis pubis and osteomyelitis of the pubic symphysis**

**Key points:**

- Systematic review of 17 case series and 10 case reports comprising 195 athletes diagnosed with osteitis pubis and treated with either conservative measures or physical therapy, local injection with corticosteroids and/or local anesthetic, dextrose prolotherapy (one small case series), surgery, or antibiotic therapy.
- The current medical literature shows weak evidence of the treatment for osteitis pubis in athletes.
- Comparative effectiveness data are needed to determine which modality provides the fastest return to a sport.

### Coombes (2010)

**Effectiveness and safety of injections for management of tendinopathy**

**Key points:**

- Systematic review of 41 trials \((n = 2672)\) on efficacy and risk of adverse events for treatment of tendinopathy by injection.
- Injections of prolotherapy effective in reducing pain (standardized mean difference [SMD] 2.62) in the intermediate term.
- Prolotherapy not as effective as sodium hyaluronate (short term SMD 3.91, intermediate term SMD 2.89), but more effective than botulinum toxin (short term SMD 1.23).

### References

**Professional society guidelines/other:**


Peer-reviewed references:


**CMS National Coverage Determinations (NCDs):**

National Coverage Determination (NCD) for Prolotherapy, Joint Sclerotherapy, and Ligamentous Injections with Sclerosing Agents (150.7). CMS website. [https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=15&ncdver=1&SearchType=Advanced&CoverageSelection=Both&NCSelection=NCA%7cCAL%7cNCD%7cMEDCAC%7cTA%7cMCD&PolicyType=Final&s=All&KeyWord=prolotherapy&KeyWordSearchType=Exact&kq=true&bc=IAAAABAAAAAAA%3d%3d&](https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=15&ncdver=1&SearchType=Advanced&CoverageSelection=Both&NCSelection=NCA%7cCAL%7cNCD%7cMEDCAC%7cTA%7cMCD&PolicyType=Final&s=All&KeyWord=prolotherapy&KeyWordSearchType=Exact&kq=true&bc=IAAAABAAAAAAA%3d%3d&). Accessed January 12, 2017.

**Local Coverage Determinations (LCDs):**

L34832 Facet Joint Injections, Medial Branch Blocks, and Facet Joint Radiofrequency Neurotomy.

L34992 Facet Joint Injections, Medial Branch Blocks, and Facet Joint Radiofrequency Neurotomy.

L34993 Facet Joint Injections, Medial Branch Blocks, and Facet Joint Radiofrequency Neurotomy.
L34995 Facet Joint Injections, Medial Branch Blocks, and Facet Joint Radiofrequency Neurotomy.

L35178 Facet Joint Injections, Medial Branch Blocks, and Facet Joint Radiofrequency Neurotomy.

L35936 Facet Joint Injections, Medial Branch Blocks, and Facet Joint Radiofrequency Neurotomy.

L35996 Facet Joint Injections, Medial Branch Blocks, and Facet Joint Radiofrequency Neurotomy.

L34218 Injections - Tendon, Ligament, Ganglion Cyst, Tunnel Syndromes and Morton's Neuroma.

L34589 Injections - Tendon, Ligament, Ganglion Cyst, Tunnel Syndromes and Morton's Neuroma.

L33622 Pain Management.

L35107 Pain Management of Peripheral Nerves by Injection.

L34293 Surgery: Lumbar Facet Blockade.

L34299 Surgery: Trigger Point Injections.

L34211 Trigger Point Injections.

L35010 Trigger Point Injections.

L34588 Trigger Points, Local Injections.

**Commonly submitted codes**

Below are the most commonly submitted codes for the service(s)/item(s) subject to this policy. This is not an exhaustive list of codes. Providers are expected to consult the appropriate coding manuals and bill accordingly.

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<thead>
<tr>
<th>CPT Codes</th>
<th>Description</th>
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<td>Injection(s), platelet rich plasma, any site, including image guidance, harvesting and preparation when performed.</td>
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<table>
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