Injectable Clostridial Collagenase for Fibroproliferative Disorders

Policy

Injectable clostridial collagenase may be considered medically necessary for the treatment of Dupuytren contracture in adult patients with a palpable cord, for up to 3 injections at intervals of at least 30 days (see the Policy Guidelines section).

Injectable clostridial collagenase is considered investigational for all other indications including, but not limited to, Peyronie disease and adhesive capsulitis.

Product name: Xiaflex® (collagenase clostridium histolyticum)

Related Policies

N/A

Policy Guidelines

Multiple injections: for Dupuytren contracture up to 2 joints in the same hand may be done during a treatment visit, consistent with U.S. Food and Drug Administration (FDA) labeling.

Coding

<table>
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<tr>
<th>CPT</th>
<th>Description</th>
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<tr>
<td>20527</td>
<td>Injection, enzyme (e.g., collagenase), palmar fascial cord (i.e., Dupuytren's contracture)</td>
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<td>26341</td>
<td>Manipulation, palmar fascial cord (i.e., Dupuytren’s cord), post enzyme injection (e.g., collagenase), single cord</td>
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<td>54200</td>
<td>Injection procedure for Peyronie disease</td>
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HCPCS

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<tr>
<td>J0775</td>
<td>Injection, collagenase clostridium histolyticum, 0.01 mg</td>
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Clostridial collagenase histolyticum is an enzyme produced by the bacterium Clostridium histolyticum that has the physiologic effect of breaking down collagen. It has been developed and marketed pharmacologically as a treatment for disorders associated with collagen overdevelopment (fibroproliferative disorders) such as Dupuytren contracture, adhesive capsulitis, and Peyronie disease. The treatment is an office-based procedure, and general anesthesia is not required.

Background
Injection with clostridial collagenase is intended to provide a nonoperative treatment option for fibroproliferative disorders. Fibrotic tissue disorders, characterized by excessive collagen deposits, can affect the musculoskeletal system, causing pain and limiting movement and reducing joint range of motion. Examples of fibroproliferative disorders include Dupuytren disease, Peyronie disease, and adhesive capsulitis.

The mechanisms that contribute to the pathology are poorly understood. In Dupuytren disease, collagen deposition in nodules and cords in the palm and fingers results in pitting of the overlying cutis and flexion contractures. The standard of care for Dupuytren disease is surgery, most commonly open fasciectomy. Other surgical procedures are percutaneous fasciotomy and needle fasciotomy. Surgery is recommended in patients with functional impairment and metacarpophalangeal joint contractures of 30° or more. There is no effective pharmacotherapy.

Peyronie disease is the development of abnormal scar tissue, or plaques, in the tunica albuginea layer of the penis causing distortion, curvature, and pain, usually during erection. It occurs in 3% to 9% of men, most commonly between the ages of 45 and 60 years. In some cases, plaque does not cause severe pain or curvature, and the condition resolves on its own. In severe cases, erectile dysfunction can occur. The goal of treatment is to reduce pain and maintain sexual function. Treatments in early stages (before calcification) include vitamin E or para-aminobenzoate tablets (e.g., Potaba), although studies of oral therapies demonstrate inconsistent benefit. Intralesional injection therapy consisting of injection of interferon-α-2b or calcium channel-blockers (e.g., verapamil) is the current standard of therapy. Surgical procedures involve the excision (removal) of hardened tissue and skin graft, the removal or pinching (plication) of tissue opposite the plaque to reduce curvature (the Nesbit procedure), a penile implant, or a combination of these.

Adhesive capsulitis or “frozen shoulder” is treated with physical therapy and mobilization in combination with analgesics or nonsteroidal anti-inflammatory drugs. Corticosteroid injection is used with caution. The prevalence of Dupuytren disease and adhesive capsulitis is estimated at 3% to 6% and 2% to 3%, respectively, in the general population and increases with advancing age. Both conditions are more common in patients with diabetes or thyroid disease. Dupuytren disease is more common in men, and adhesive capsulitis more common in women.

Regulatory Status

| Table 1. FDA-Approval History For Clostridial Collagenase (Xiaflex®)(3) |
|---------------------------------|-----------------|-----------------|---------------------------------|
| **Indication**                  | **Approved**    | **Initial Indication** | **Additional Information** |
| Dupuytren contracture           | 2010            | Treatment of adult patients with Dupuytren contracture with a palpable cord | Approval accompanied by REMS. The manufacturer must:  
  o Evaluate and mitigate risks and serious adverse events.  
  o Instruct health care providers on procedure to inject Xiaflex and perform finger extension procedures.  
  o Inform patients of potential risks of treatment.  
  In 2014, indication expanded: up to 2 joints in the same hand may be treated during a treatment visit. |
| Peyronie                        | 2013            | Treatment of men with a palpable plaque | Approval accompanied by black box |
Rationale

<table>
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<th>Populations</th>
<th>Interventions</th>
<th>Comparators</th>
<th>Outcomes</th>
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<td>Individuals: With Dupuytren contracture</td>
<td>Interventions of interest are: • Local clostridial collagenase injection(s)</td>
<td>Comparators of interest are: • No therapy/observation • Surgical therapy</td>
<td>Relevant outcomes include: • Symptoms • Change in disease status • Functional outcomes • Quality of life</td>
</tr>
<tr>
<td>Individuals: With Peyronie disease</td>
<td>Interventions of interest are: • Local clostridial collagenase injection(s)</td>
<td>Comparators of interest are: • No therapy/observation • Oral medications • Other intralesional treatments (e.g., verapamil)</td>
<td>Relevant outcomes include: • Symptoms • Change in disease status • Functional outcomes • Quality of life</td>
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Scope

Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.

Benefit Application

Some plans may require prior authorization of collagenase clostridium histolyticum. For questions about benefit information, providers should contact customer service using the telephone number on the back of the member's identification card.
This policy was originally created in 2010 and has been regularly updated with searches of the MEDLINE database. The most recent literature review covered the period through August 2016. Following is a summary of the key findings to date.

### Dupuytren Disease (Dupuytren Contracture)

#### Systematic reviews

In 2016, Smeraglia et al reported results of a systematic review of studies reporting on clostridial collagenase injections for Dupuytren contracture. The review included 43 studies that compared collagenase with placebo, open fasciotomy, or needle aponeurotomy. The authors noted that the evidence for the efficacy of collagenase injection was not robust, and there were no head-to-head comparisons with surgical interventions. A meta-analysis was performed, but the results should be interpreted with caution due to the limited number of studies and the heterogeneity of the interventions.

In 2015, Brazzelli et al reported on a Health Technology Assessment including a systematic review and economic evaluation of clostridial collagenase for the treatment of Dupuytren contracture. The review included RCTs, nonrandomized comparative studies, and observational studies with collagenase and/or surgical interventions, in patients with a palpable Dupuytren cord. The authors included the following studies: “Five RCTs comparing collagenase with placebo (493 participants), three RCTs comparing surgical techniques (334 participants), two non-randomised studies comparing collagenase and surgery (105 participants), five non-randomised [sic] comparative studies assessing various surgical procedures (3571 participants) and 15 collagenase case series (3154 participants).” A meta-analysis was used when there was adequate data for analysis. In addition, a de novo decision analytic model from the perspective of the U.K. National Health Service and Personal Social Services was developed to assess the cost-utility of various treatment strategies for Dupuytren contracture. In summary of the study’s meta-analysis, no head-to-head RCTs of clostridial collagenase compared with surgery were identified. Of the 5 RCTs comparing collagenase with placebo, 3 were included in a meta-analysis. In pooled analysis, the proportion of all first, first metacarpophalangeal (MCP), first proximal interphalangeal (PIP) joints achieving clinical success favored clostridial collagenase (relative [RR], 10.21; 95% confidence interval [CI], 5.29 to 19.69; I2=0%; RR=10.27; 95% CI, 4.88 to 21.65; I2=0%; RR=6.90; 95% CI, 4.28 to 11.12; I2=0%, respectively). However, rates of local adverse events were higher in clostridial collagenase-treated patients.

Chen et al published a systematic review in 2011 of various treatments for Dupuytren contracture. Studies published through December 2010 were examined and included 4 prospective studies (including 2 randomized studies) on collagenase injections, 6 studies on open partial fasciectomy (including 2 randomized studies), and 3 studies on needle aponeurotomy. Sample sizes for all studies included in the review ranged from 13 to 261 patients. The authors found recurrence rates for collagenase injections (mean follow-up time range, 120 days to 4 years) ranged from 10% to 31%. Needle aponeurotomy had the highest recurrence rates (50%-58%; mean follow-up, 3-5 years), which were significantly higher than the open partial fasciectomy recurrence rates (12%-39%; mean follow-up time, 1.5-7.3 years). Additionally, open partial fasciectomy recurrence rates were significantly higher than collagenase injection. Complications occurred most often with open partial fasciectomy, although 2 cord ruptures were reported with collagenase injection. The authors concluded further studies are needed to understand the long-term outcomes of these interventions and how to address contracture recurrence. It was also noted that it is unclear whether collagenase injection can be used for Dupuytren revision.

In 2014, Peimer et al. summarized the safety and tolerability of clostridial collagenase or surgical treatment (fasciectomy) for Dupuytren contracture. The safety of clostridial collagenase was based on 11 clinical trials, including 1082 patients, while the safety of fasciectomy was based on 48 European studies, including 7,727 patients. Compared with rates reported after fasciectomy, clostridial collagenase–treated patients had lower rates of nerve injury (median, 0% vs 3.8%), neurapraxia (4.4% vs 9.4%), complex regional pain syndrome (0.1% vs 4.5%), and arterial injury (0% vs 5.5%), but higher reported rates of tendon injury (0.3% vs 0.1%), skin injury (16.2% vs 2.8%), and hematoma (77.75% vs 2%), all respectively. Pooled estimates and statistical comparisons were not reported.
**Randomized Controlled Trials**

This review identified 5 publications from three unique double-blind, randomized controlled trials (RCTs) (including two follow-up RCT extension studies), all sponsored by the manufacturer (Auxilium Pharmaceuticals).

In 2009, Hurst et al. published results from the Collagenase Option for Reduction of Dupuytren’s I (CORD I) study, a randomized, double-blind, placebo-controlled, multicenter trial (16 sites) of collagenase C histolyticum for Dupuytren contracture with 308 subjects with joint contractures of 20° or more. This study was included in the Chen review previously described. (6) Joints were stratified according to type (metacarpophalangeal [MCP] joints or proximal interphalangeal joint [PIP]) and severity of contracture; they were randomly assigned in a 2:1 ratio to receive up to 3 injections of either collagenase or placebo in the contracted collagen cord at 30-day intervals. Secondary and tertiary joints were identified for possible subsequent injections. Joints were manipulated one day after injection if necessary. The primary endpoint was reduction in contracture to 0° to 5° of full extension 30 days after last injection. Twenty-six secondary endpoints were also evaluated. Recurrence of contracture was defined as an increase in joint contracture of 20° or more and was considered an adverse event (AE). Efficacy results were based on 306 primary joints: 203 injected with collagenase and 103 injected with placebo. In the collagenase-treated group, 130 of 203 (64%) cords met the primary endpoint versus 7 of 103 (6.8%) placebo-injected cords (p<0.001). More than half of the collagenase-injected joints that did not meet the primary endpoint did not receive the maximum allowable number of injections, most commonly because a cord could not be palpated or the patient was satisfied with the result. Median time to reach the primary endpoint for collagenase-treated joints was 56 days. At the 90-day visit, there was no recurrence of contracture in collagenase-treated primary joints that had reached the primary endpoint.

When analyzed by joint type, more collagenase-treated joints achieved the primary endpoint than placebo (MCP, 76.7% vs. 7.2%; proximal PIP joint, 40.9% vs. 5.9%, both respectively; p<0.001 for both comparisons). Mean change in contracture from baseline to 30 days after last injection was 48.0° to 7.2° in the collagen-injected MCP joints and 45.4° to 43.1° in the placebo-injected MCP joints. Thirty days after last injection, 84.7% of collagenase-injected joints versus 11.7% of placebo-injected joints showed clinical improvement. Results were better in MCP joints than in PIP joints: 94.0% versus 67.1%, respectively, in the collagenase group, and 11.6% versus 11.8%, respectively, in the placebo group. Overall, 96.6% of patients who received collagenase reported at least one treatment-related adverse event. They had significantly more injection- and manipulation-related events, such as contusion, hemorrhage, injection-site pain, upper-extremity pain, and lymphadenopathy (p ≤0.02), than patients who received placebo injection. Most were mild or moderate in intensity; however, 20 patients in the collagenase group and 2 in the placebo group reported events that were severe in intensity. Three severe AEs were considered to be treatment-related: a case of complex regional pain syndrome and 2 tendon ruptures, both requiring surgical procedures. The CORD I authors noted that the timeframe of this study was insufficient to assess recurrence, and they could not make any claims about this outcome. In 2011, Witthaut et al. reported on range of motion (ROM) outcomes from the CORD I study. (9) On day 30, mean ROM increased from 43.9° to 80.7° in joints treated with collagenase. In the joints treated with placebo, mean ROM increased 45.3° to 49.5° on day 30. Using regression models to create a ROM severity classification, the authors reported that joints treated with collagenase had a significant mean increase in ROM of 36.7° (p<0.001), whereas joints treated with placebo had a nonsignificant mean increase of 4.0°.

In a letter to the editor in response to publication of the study, Holzer and Holzer commented that successful treatment of Dupuytren disease correlates with the percentage of excised Dupuytren tissue and the extent of the intervention. (10) They cautioned that the value of collagenase injection must be confirmed in a long-term follow-up study that focuses on the recurrence rate.

In 2010, Gilpin et al. published results of the CORD II study. (11) In this study, 66 patients were randomized to receive collagenase injection (45 cords) or placebo (21 cords) in the 90-day, double-blind phase followed by an open-label phase of 9 months. The authors reported that, within 30 days, collagenase injections resulted in significantly more cord contracture improvement from baseline to within 0° to 5° of normal than placebo (44.4% vs. 4.8%, respectively). Results after the open-label treatment were reported to be similar to the double-blind phase. Recurrence of contracture (defined as increase of contracture to ≥20° did not occur during the 12-month follow-up. All study participants experienced mild adverse events (e.g., swelling and pain at injection site). Three serious adverse effects related to the treatment were reported. A flexion pulley rupture of the left small finger occurred in one patient while rapid thickening of the treated cord and sensory abnormalities occurred in another patient.
In 2014, McGrouther et al. reported results from a post hoc subgroup analysis of the randomized and open-label phases CORD I and II studies to evaluate the efficacy and safety of clostridial collagenase in the subgroup of 58 Dupuytren contracture patients (67 joints) with up to 2 joints affected and moderate disease, according to British Society of Surgery of the Hand classification. (12) Of the subgroup, 82% met the primary end point of clinical success, defined as a reduction in contracture to within 5° of full extension 30 days after the last injection. Recurrence of the contracture (defined as an increase in joint contracture to ≥20° in the presence of a palpable cord in joints that had previously had clinical success) occurred in 3.8% of joints treated. Fifty-five patients (94.8%) developed treatment-related adverse events, all of which were considered mild (e.g., pain and swelling at the injection site).

In 2007, Badalamente and Hurst reported on patients who participated in a double-blind Phase III RCT comparing collagenase and placebo injections. (13) During the double-blind and open-label phases, 62 joints (31 MCP, 31 PIP) were treated in 35 patients. Fifty-four (87%) were clinical successes. Twenty-seven joints were followed for 24 months. Over the 24 months after the last injection, 5 joints had recurrences (1 MCP, 4 PIP), 1 before 12 months, 2 at 12 months, and 2 at 24 months after treatment. Three of these patients underwent fasciectomy. The most common AEs were local reactions to injections. The limited patient follow-up makes it difficult to reach conclusions from this study.

In 2014, Raven et al. published a subgroup analysis of data pooled from the previously described 3 RCTs (CORD I, CORD II, Badalamente and Hurst) of collagenase treatment of Dupuytren-related contractures. (14) This analysis included 271 patients with MCP (n=167) or PIP (n=104) joint contractures of ≥20° or more treated with collagenase injections (0.58 mg collagenase per injection). Subgroups included age, sex, and diabetes status. Endpoints included rate of clinical success (reduction in contracture to 0°-5° of normal) and percentage of AEs. There were no significant differences in clinical success by age, diabetes status, or sex, with 63% of cases reaching the end point. In addition, there were no differences in complication rates among the subgroups, with peripheral edema, contusion, and injection-site hemorrhage being most common. (14)

**Nonrandomized Comparative Studies**

Since the publication of the RCTs previously described, several smaller nonrandomized studies have compared clostridial collagenase with surgical procedures for the treatment of Dupuytren contracture.

Naam et al. conducted a retrospective comparison of patients with Dupuytren contracture affecting at least 1 joint with a palpable cord who underwent clostridial collagenase injections (N=25) or fasciectomy (N=21). (15) Some patients who received clostridial collagenase injections were enrolled in the JOINT 1 study, described next. Over an average follow-up of 32 months for patients treated with clostridial collagenase and 39 months for those treated with fasciectomy, mean post-treatment contracture, decrease in contracture from baseline, and increase in ROM from baseline at the MCP and PIP joints did not differ significantly. Mean post-treatment ROM at the MCP joint was significantly higher in the clostridial collagenase–treated patients (90.7° vs 83.3° p=0.02), while the post-treatment ROM at the PIP was higher in the fasciectomy–treated patients, although the difference was not statistically significant (67.5° vs. 88.8° p=0.06). Complication rates were similar in both groups, although patients who received clostridial collagenase returned more quickly to work and to normal daily activities.

In a small study from a single U.K. center, Povlsen et al. prospectively assessed outcomes for patients with single-digit Dupuytren contracture who underwent open fasciectomy (N=10) or clostridial collagenase injection followed by manipulation (N=10). (16) Total active movement at the PIP joint and at the MCP and PIP joints combined were statistically better in the clostridial collagenase group (p=0.01 and p<0.025, respectively) in the short term (i.e., days) after the procedure. Longer term follow-up was not reported.

Zhou et al. compared outcomes for patients who underwent clostridial collagenase injection or limited fasciectomy for Dupuytren contracture at 7 sites in the Netherlands. (17) A total of 218 subjects met inclusion criteria (104 treated with clostridial collagenase, 114 treated with limited fasciectomy). After propensity score matching, the final analysis group included 66 subjects with each treatment. At last follow-up at 6 to 12 weeks postprocedure, the residual contracture for affected MCP joints did not differ significantly between groups (9° for clostridial collagenase vs. 8° for limited fasciectomy, p=0.095), while affected PIP joints had significantly worse residual contracture in the collagenase group (25° vs. 15°, p=0.010). Fewer adverse events occurred among clostridial collagenase–treated subjects.

**Noncomparative Studies**
Noncomparative studies are included to provide data on adverse event rates after clostridial collagenase injections. A number of single-arm studies have reported outcomes after clostridial collagenase injections for Dupuytren contracture, the largest of which were the JOINT I, JOINT II, and CORDLESS studies.

In 2013, Witthaut et al. published the findings from two concurrent open-label, single-arm studies (JOINT I, JOINT II) designed to evaluate the efficacy and safety of collagenase injections (0.58 mg collagenase per injection) used to reduce the degree of contracture in patients with advanced Dupuytren contracture at 9 months of follow-up.18 The primary end point was clinical success, defined as a reduction in contracture to within 0° to 5° of full extension 30 days after the last injection. A secondary endpoint was clinical improvement, defined as 50% or more reduction from baseline contracture. Dupuytren cords affecting 879 joints (531 MCP, 348 PIP) in 587 patients were administered collagenase injections at(14) American (JOINT I) and 20 Australian/European (JOINT II) sites. Similar results were reported in both studies. Seventy-one percent of joints (n=625) did not require a second injection, and 89% of joints did not require a third injection. Clinical success was achieved in 497 (57%) of treated joints using 1.2 (SD=0.5) collagenase injections per cord. More MCP than PIP joints achieved clinical success (70% and 37%, respectively) or clinical improvement (89% and 58%, respectively). For joints not achieving clinical success and not receiving the maximum 3 injections (128 MCP, 173 PIP joint), reasons included no palpable cord (MCP joint, 52%; PIP joint, 44%); injections in other cords reached the protocol-specified per-patient maximum of 5 per patient (MCP joint, 19%; PIP joint, 21%); and satisfied with response (MCP joint, 8%; PIP joint, 9%). When data from JOINT I and II were pooled to evaluate clinical success by contracture severity, the MCP and PIP joints with less contracture severity (i.e., ≤ 50° and ≤ 40°, respectively) showed a better response than more severely contracted joints. After 9 months of follow-up, 71% of patients were “very satisfied” and 21% “quite satisfied” with collagenase treatment, using a 5-point Likert-type scale. For physician ratings of improvement, 47% rated change from baseline as “very much improved,” and 35% as “much improved” using a 7-point scale.18

The relatively short-term (9-month) follow-up in these two JOINT studies limits the ability to make conclusions regarding long-term outcomes, including the likelihood of recurrence. Patients who achieved clinical success in the two JOINT studies had the option to enroll in a 5-year follow-up study, which also included patients from the two CORD studies previously reviewed.

In 2013, Peimer et al. published interim data after the third year of the above-mentioned 5-year follow-up study, Collagenase Option for Reduction of Dupuytren Long-Term Evaluation of Safety Study (CORDLESS).19 Of 1,080 collagenase-treated joints, 623 (451 MCP, 172 PIP) had achieved 0° to 5° contracture in the original studies. Recurrence occurred in 35% of the successfully treated joints over the 3-year follow-up period. No long-term complications attributed to collagenase injections were reported during this follow-up period.18 Five-year follow-up from the CORDLESS registry were reported in 2015.19 Recurrence occurred in 47% (291/623) of successfully treated joints.

Badalamente et al. published a pooled analysis of data from the CORD I and II trials (described in Randomized Controlled Trials section above) and the JOINT I and II trials reporting on outcomes for clostridial collagenase for PIP contractures.21 The pooled analysis included 644 PIP joints in 506 patients, of which 60% (384 joints), 24% (154 joints), and 16% (100 joints) were treated with 1, 2, and 3 injections, respectively. Clinical success (0°-5° of full extension) occurred in 27% of joints after 1 injection and 34% after the last injection. Clinical improvement occurred in 49% of joints after 1 injection and 585 after the last injection. Six treatment-related serious adverse events occurred, including 2 tendon ruptures and 1 case each of tendon injury, complex regional pain syndrome, finger deformity, and tendonitis.

In 2015, Gaston et al. reported safety and efficacy outcomes of a Phase 3b, open-label study of the concurrent administration of 2 clostridial collagenase injections into cords in the same hand to treat 2 joints with Dupuytren contractures.22 The study enrolled 715 patients with 725 joint pairs treated; 3 patients were lost to follow-up, 3 patients withdrew consent, and 1 patient did not have a post-baseline efficacy assessment. Seven hundred fourteen patients with 724 joint pairs were included in a modified intention-to-treat efficacy analysis. Joint pairs treated included MCP and PIP joints on the same finger, 2 MCP joints on different fingers, 2 PIP joints on different fingers, and 1 MCP and 1 PIP joint on different fingers in 48%, 34%, 10%, and 8% of subjects, respectively. The percent improvement in fixed flexion contracture was 72%, 84%, 60%, and 68% in patients who had treatment of the MCP/PIP joints (same finger), 2 MCP joints (different fingers), 2 PIP joints (different fingers), and MCP/PIP joints (different fingers), respectively. At least 1 treatment-related adverse event occurred in 95% of subjects, most of which were mild or moderate. Six patients had treatment-related or possibly treatment-related serious adverse events.

A number of other smaller single-arm studies have been published, with sample sizes ranging from 23 to 254, and
generally with shorter term follow-up (=6 to 15 months). (23-29) One of these studies, by Watt et al., reported on 23 patients, 8 of whom had long-term follow-up to 8 years.(23) Among those with isolated MCP contracture (n=6), 4 experienced recurrence by 8 years, while 2 of 2 patients with isolated PIP contracture experienced recurrence by 8 years.

Section Summary
The most direct evidence related to the use of clostridial collagenase for Dupuytren contractures comes from several RCTs, which compare clostridial collagenase with placebo injections, and generally show high rates of contracture resolution. This evidence is supported by nonrandomized comparative studies comparing clostridial collagenase to surgery. Some studies report similar outcomes with faster return-to-work and return-to-usual activities rates with clostridial collagenase, but 1 study reported poorer contraction improvement but lower adverse event rates with clostridial collagenase. Rates of local AEs, including local swelling, pain, and ecchymosis, are generally high.

Peyronie Disease
Systematic reviews
In 2015, Carson et al reported a pooled analysis of 6 clinical studies to evaluate safety outcomes for clostridial collagenase for Peyronie disease.(30) Studies included were phase 2 and 3 industry-sponsored trials of clostridial collagenase, which are included in the Randomized Controlled Trials section below. A total of 1044 patients were included in the pooled safety analysis, of whom 85.8% had a treatment-related adverse event, most of which (75.2%) were mild or moderate in severity. Approximately 1% (n=9) of patients had a treatment-related serious adverse event, including 5 cases of penile hematoma and 4 cases of corporal rupture.

In 2007, Russell et al. conducted a systematic review of plaque injection therapy for Peyronie disease, which included 2 studies of collagenase.(31) Both articles, one RCT and one rated as a lower level study and published in 1985 and 1993,(32,33) reported positive treatment outcomes. However, more recent RCT evidence is available that provides more direct evidence on the efficacy on clostridial collagenase injections for Peyronie disease.

Randomized Controlled Trials
A 1993 randomized, placebo-controlled, double-blind study with 49 subjects reported by Gelbard et al., compared the effects of collagenase and placebo on plaque size and penile deformity. For the group as a whole, treatment with collagenase was significantly more effective (p<0.007). Patients with lesser deformity responded more favorably to treatment.(33)

In 2013, Gelbard et al. published the results of 2 double-blind, placebo-controlled RCTs, IMPRESS (Investigation for Maximal Peyronie’s Reduction Efficacy and Safety Studies) I and II, which examined the clinical efficacy and safety of collagenase injections in subjects with Peyronie disease.(34) These RCTs were sponsored by the manufacturer (Auxilium Pharmaceuticals), the findings of which were submitted to FDA in support of their biologics license application. These 2 studies examined collagenase injections in 417 and 415 participants, respectively, through a maximum of 4 treatment cycles, each separated by 6 weeks (for up to 8 injections of 0.58 mg collagenase). Men were stratified by baseline penile curvature (30° to 60° vs 61° to 90°) and randomized to collagenase injections or placebo in a 2:1 ratio. The primary outcomes were the percent change in the penile curvature abnormality and the change in the Peyronie’s Disease Questionnaire (PDQ; developed by manufacturer) Symptoms Bother score from baseline to 52 weeks. Data from the IMPRESS I and II studies were combined. Participants treated with collagenase injections showed a mean percent improvement in penile curvature abnormality of 34%, compared with 18% improvement in penile curvature in the placebo group; this change in curvature and the percent improvement in the collagenase group were significantly greater than in the placebo group (each p<0.001). The mean change in the PDQ symptom bother domain score was significantly improved in the collagenase group than in the placebo group (-2.8±3.8 vs. -1.8±3.5, p=0.004). The most frequently reported complications (≥45%) in the collagenase-treated group included penile ecchymosis, penile swelling, and penile pain. Six participants experienced treatment-related serious adverse events, including corporeal rupture in 3 cases and penile hematoma in the other 3 cases. The 3 corporeal ruptures and 1 hematoma were successfully repaired surgically. Of the 2 remaining penile hematomas, 1 case was successfully resolved without intervention and the other resolved with aspiration.(34)

In 2015, Lipshultz et al. reported post hoc subgroup analyses from the combined data from the IMPRESS I and II
This analysis included a modified intention-to-treat population of 612 subjects who had both a penile curvature deformity measurement and a PDQ response at baseline and at least 1 subsequent time point after the first injection of clostridial collagenase. Subgroups included those stratified based on duration of illness, degree of plaque calcification, and International Index of Erectile Function (IIEF) severity score. Reductions in penile curvature deformity occurred in all groups; penile curvature deformity reductions were significantly greater with clostridial collagenase than with placebo for those with baseline penile curvature 30° to 60° and 61° to 90°, disease duration over 2 years, no calcification, and IIEF severity score of 17 or greater. Peyronie disease symptom bother reductions were significantly greater with clostridial collagenase than with placebo for those with penile curvature 30° to 60°, disease duration over 4 years, no calcification, and IIEF scores 1 to 5 (no sexual activity) and 17 or greater. However, generalization of this analysis is limited by its post hoc design and small subgroups.

The development and validation of the PDQ has been described by Hellstrom et al. in 2013. Investigators developed the PDQ to quantitatively assess the symptoms and psychosexual consequences of Peyronie disease by provided 3 subscale domain scores, including psychological and physical symptoms (6 items), penile pain (3 items), and symptom bother (4 scored items and 2 yes/no questions). Questions were evaluated based on baseline data for 679 patients in IMPRESS I and II who had been sexually active in the last 3 months (81% of the total 836 enrolled). PDQ domain scores did not significantly differentiate between patients with a different extent of curvature abnormality. Coyne et al. assessed the responsiveness of the PDQ to changes in Peyronie disease symptoms in subjects from the IMPRESS I and II trials. In this group, PDQ Psychological and Physical Symptoms and Symptom Bother subscales significantly discriminated patient improvement in responses to a global assessment of the PDQ and degree of penile curvature at weeks 24 and 52.

Noncomparative Studies
Case series have reported outcomes from the treatment of clostridial collagenase for Peyronie disease. Many of these are small (n≈20) or from older treatment years such as 1985 that limits the utility of the results. However, some of the larger studies provide outcome data on adverse events after clostridial collagenase treatment for Peyronie disease.

Carson et al. reported serious and nonserious adverse events after clostridial collagenase for Peyronie disease in a pooled analysis of clostridial collagenase recipients from 6 trials (N=1044). Of treated patients, 85.8% (n=896) reported at least 1 treatment-related adverse event, most frequently penile hematoma in more than 25.0% of patients. Nine patients (0.9%) had a treatment-related serious adverse event involving significant penile hematoma or corporal rupture.

A single-arm, open-label trial reported by Levine et al described outcomes for 238 subjects with Peyronie disease treated with clostridial collagenase with both a penile curvature measurement and a PDQ response at baseline and at least 1 subsequent time point (of 347 total subjects treated). The degree of penile curvature improved from baseline to week 36 (34.4%; 95% CI: 31.2 to 37.6%) and PDQ Symptom Bother score (mean change, 3.3; 95% CI: 2.8 to 3.7). However, the lack of comparison group and exclusion of a high proportion of subjects missing follow-up data limit conclusions that can be drawn.

Section Summary
The most direct evidence related to the use of clostridial collagenase injections to treat Peyronie disease comes from 2 industry-sponsored RCTs that compared clostridial collagenase with placebo. Clostridial collagenase–treated subjects demonstrated significant improvements in penile curvature (absolute percentage improvement, 16%) and reported improvements their degree of bother related to the disease. However, it is not clear that these improvements in curvature or in the degree of symptom bother translated into differences in patient outcomes, and whether the benefit of treatment exceeds the risks.

Adhesive Capsulitis
No studies including patients with adhesive capsulitis were identified in the literature search.

Ongoing and Unpublished Clinical Trials
Some trials that might influence this policy are listed in Table 2.
Table 2. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
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<tr>
<td>Ongoing</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>NCT01538017</td>
<td>Comparing Injectable Collagenase (CI) and Percutaneous Needle Fasciotomy (PNF) for Dupuytren's Contracture (DC) Affecting Proximal Interphalangeal Joints (PIP). A Randomised Controlled Trial.</td>
<td>50</td>
<td>Nov 2015</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unpublished - completed</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT01483963*</td>
<td>A Phase IIa, Open-label, Dose-ranging Study of the Safety and Effectiveness of AA4500 for the Treatment of Adhesive Capsulitis of the Shoulder</td>
<td>50</td>
<td>Feb 2013</td>
</tr>
<tr>
<td>NCT02006719*</td>
<td>A Randomized, Double-blind, Placebo-controlled Study of the Safety and Efficacy of AA4500 for the Treatment of Adhesive Capsulitis of the Shoulder</td>
<td>322</td>
<td>Dec 2014</td>
</tr>
<tr>
<td>NCT02193828*</td>
<td>A Phase IIa, Double-blind, Randomized, Placebo-Controlled, Dose-Ranging Study to Evaluate the Safety and Effectiveness of AA4500 in the Treatment of Dupuytren's Disease Nodules</td>
<td>76</td>
<td>Mar 2014</td>
</tr>
<tr>
<td>NCT02267460*</td>
<td>A Phase IIIb, Open-label Pilot Study to Evaluate the Safety and Effectiveness of up to Four Treatment Cycles of AA4500 in Combination With the ErecAid® Esteem® Manual Vacuum Therapy System in Men With Peyronie's Disease</td>
<td>30</td>
<td>Mar 2016</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.
* Denotes industry-sponsored or cosponsored trial.

Summary of Evidence

The evidence for the use of clostridial collagenase in individuals with Dupuytren contracture includes several placebo-controlled, randomized trials, nonrandomized comparative studies, and single-arm studies along with systematic reviews of these studies. Relevant outcomes are symptoms, change in disease status, functional outcomes, and quality of life. The evidence from clinical trials suggests that injectable clostridial collagenase provides short-term release of contracture. A comparison of overall outcomes compared with surgical intervention may be useful; however, randomized studies with direct comparisons are not available. Some nonrandomized studies comparing clostridial collagenase with surgery report similar outcomes with faster return-to-work and return-to-usual activities rates with clostridial collagenase, but 1 study reported poorer contraction improvement but lower adverse event rates. Evidence on long-term recurrence rates is somewhat limited, but 3- and 5-year follow-ups from 1 large registry reported high recurrence rates (47% at 5 years). Although clostridial collagenase is associated with the potential benefit of being a less-invasive treatment for Dupuytren contracture, gaps in the evidence base related to treatment durability exist. The evidence is insufficient to determine the effects of the technology on health outcomes.

The evidence for the use of clostridial collagenase in individuals with Peyronie disease includes 2 randomized trials and several noncomparative studies. Relevant outcomes are symptoms, change in disease status, functional outcomes, and quality of life. The available double-blind, placebo-controlled randomized trials have demonstrated short-term improvement in penile curvature and self-reported distress from symptoms related to Peyronie disease. However, evidence demonstrating health outcome improvements are lacking. In addition, studies comparing clostridial collagenase with other therapies for Peyronie disease are lacking. The evidence is insufficient to determine the effects of the technology on health outcomes.

The evidence for the use of clostridial collagenase in individuals with adhesive capsulitis is very limited. Relevant outcomes are symptoms, change in disease status, functional outcomes, and quality of life. No published literature that addressed the treatment of adhesive capsulitis with clostridial collagenase was identified. The evidence is insufficient to determine the effects of the technology on health outcomes.

Clinical Input Received from Physician Specialty Societies and Academic Medical Centers

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not...
represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

2011 Input
In response to requests, input was received from 2 physician specialty societies (2 reviews) and 5 academic medical centers (6 reviews) while this policy was under review in 2011. Two reviewers indicated injectable clostridium collagenase is investigational for the treatment of Dupuytren contracture, noting lack of long-term data and head-to-head trials comparing collagenase with surgical options. However, despite considering this treatment investigational due to insufficient long-term evidence of effectiveness, one reviewer noted that injectable clostridial collagenase for Dupuytren contracture is approved by the U.S. Food and Drug Administration, and there is evidence of short-to-medium-term effectiveness available. Five reviewers indicated injectable clostridial collagenase for Dupuytren contracture may be considered medically necessary. These reviewers noted this is a treatment alternative to surgery. This was considered to be near-uniform support for the medical necessity of injectable clostridial collagenase for the treatment of Dupuytren contracture.

Four reviewers agreed that injectable clostridium collagenase is investigational for the treatment of Peyronie disease. One of these reviewers also commented that, while this treatment is considered investigational, it may be indicated for Peyronie disease when it is bothersome, noting that surgery is intrusive. Four reviewers also agreed injectable clostridium collagenase is investigational for the treatment of adhesive capsulitis. Finally, 6 reviewers agreed injectable clostridium collagenase is investigational for all other indications.

2010 Input
In response to requests, input was received from 6 academic medical centers while this policy was under review in 2010. The input was mixed, with half those providing input agreeing that use of this agent is investigational. While there was support for use in Dupuytren contracture, comments were made about the limited amount of data on long-term outcomes and durability.

Practice Guidelines and Position Statements

International Society for Sexual Medicine
Ralph et al. developed guidelines for the treatment of Peyronie disease in 2010.(40) These guidelines indicate surgery is the treatment of choice, although conservative management is an appropriate option.

American Urological Association
In 2015, the American Urological Association (AUA) issued a guideline for the diagnosis and treatment of Peyronie disease.(41) For patients with stable Peyronie disease, penile curvature greater than 30° and less than 90°, and intact erectile function (with or without the use of medications), AUA recommends intraligamental collagenase clostridium histolyticum in combination with modeling (Moderate recommendation; Evidence Strength Grade B).

European Association of Urology
The 2012 European Association of Urology guidelines on penile curvature indicate injectable collagenase is a treatment option for Peyronie disease based on evidence rated as Level 2b (“Evidence obtained from at least one other type of well-designed quasi-experimental study”) and Grade C (“Made despite the absence of directly applicable clinical studies of good quality”).(42)

National Institute for Health Research
In 2012, the National Institute for Health Research published a Health Technology Assessment (HTA) on the management of frozen shoulder.(43) In this HTA, collagenase injections were not included in the treatments considered for frozen shoulder.

U.S. Preventive Services Task Force Recommendations
Not applicable.
Medicare National Coverage
There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

References


Appendix

N/A

History

<table>
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<tr>
<th>Date</th>
<th>Reason</th>
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</thead>
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<tr>
<td>11/11/13</td>
<td>New Policy. Policy replaces 5.01.524. Considered medically necessary to treat Dupuytren’s contracture in adult patients when criteria are met.</td>
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<tr>
<td>12/17/14</td>
<td>Annual Review. Policy updated with literature review through September 5, 2014. References 3, 5, 10, 13-14, 17-22, 27 added; others renumbered/removed. Rationale section reorganized. Policy statements unchanged. ICD-9 and ICD-10 diagnosis and procedure codes removed; these do not relate to policy adjudication.</td>
</tr>
<tr>
<td>11/08/16</td>
<td>Annual review. Policy updated with literature review through August 2016; references added. Policy statements unchanged.</td>
</tr>
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</table>

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