Injectable Clostridial Collagenase for Fibroproliferative Disorders

Policy Number: 5.01.19
Origination: 01/2011
Last Review: 12/2019
Next Review: 12/2020

Policy
Blue Cross and Blue Shield of Kansas City (Blue KC) will provide coverage for injectable clostridial collagenase when it is determined to be medically necessary because the criteria shown below are met.

When Policy Topic is covered
Injectable clostridial collagenase for the treatment of Dupuytren’s contracture in adult patients with a palpable cord may be considered medically necessary, for up to 3 injections at intervals of at least 30 days.

Injectable clostridial collagenase for the treatment of Peyronie disease in adult male patients with a palpable plaque and curvature deformity of at least 30 degrees at the start of therapy may be considered medically necessary, for up to 2 injections at least 1-3 days apart.

When Policy Topic is not covered
Injectable clostridial collagenase is considered investigational for all other indications including, but not limited to, adhesive capsulitis

Considerations
This Blue Cross and Blue Shield of Kansas City policy statement is consistent with the Blue Cross and Blue Shield Association Policy 5.01.19

Description of Procedure or Service
Clostridial collagenase is a bacterial collagenase derived from *Clostridium histolyticum* which has been evaluated for the treatment of fibroproliferative disorders such as Dupuytren contracture and Peyronie disease.

*FDA-approved uses:*

**Dupuytren contracture:**

*Initial dosage:*
0.58 mg per injection into a palpable cord with a contracture of an metacarpophalangeal (MP) joint or a proximal interphalangeal (PIP) joint. Perform up to 2 injections in the same hand during a treatment. Two palpable cords affecting 2 joints may be injected or 1 palpable cord affecting 2 joints in the same finger may be injected at 2 locations during a treatment visit. If a contracture persists, perform a finger extension procedure 24 to 72 hours after injection to facilitate cord disruption

*Repeat dosages:*
Four weeks after the injection and finger extension procedure, if an MP or a PIP contracture remains, the cord may be reinjected with a single dose of 0.58 mg, and the finger extension procedure may be repeated (approximately 24 to 72 hours after injection).

Injections and finger extension procedures may be administered up to 3 times per cord at approximately 4-week intervals
**Peyronie disease:**
If more than 1 plaque is present, inject into the plaque causing the curvature deformity

**Initial dosage:**
Inject 0.58 mg into a Peyronie plaque; repeat injection 1 to 3 days later. A penile modeling procedure should be performed 1 to 3 days after the second injection

**Repeat dosages:**
Administer a second treatment cycle (two 0.58 mg injections 1 to 3 days apart, followed by a penile modeling procedure 1 to 3 days after the second injection) in approximately 6 weeks if needed (maximum, 4 treatment cycles [a total of 8 injection procedures and 4 penile modeling procedures]). Do not administer subsequent treatment cycles if the curvature deformity is less than 15 degrees after a treatment cycle or if the health care provider determines that further treatment is not indicated.

The safety of more than 1 treatment course (ie, 4 treatment cycles) is not known

For patients with Dupuytren contracture, 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. Potentially serious adverse events (AEs) also warrant further investigation, and evidence on long-term recurrence rates is limited. While gaps in the evidence base remain, this may be an appropriate treatment option in adult patients with a palpable cord based on short-term evidence of effectiveness and a preponderance of agreement from clinical input. Therefore, injectable clostridial collagenase may be considered medically necessary as an alternative to surgical options.

For other disorders, there is less evidence. Five studies, including 2 manufacturer-sponsored double-blind, placebo-controlled randomized trials, have demonstrated short-term improvement in penile curvature and self-reported distress from Peyronie-related symptoms in patients with Peyronie disease. However, evidence demonstrating health outcome improvements is lacking, as are comparisons with current treatments. Clostridial collagenase treatment for Peyronie plaques is associated with relatively high rates of risk for significant local AEs. No published literature that addressed the treatment of adhesive capsulitis with clostridial collagenase was identified. Based on the available evidence and clinical input, injection of clostridial collagenase is considered investigational for all other treatment indications, including Peyronie disease and adhesive capsulitis.

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

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 fasciectomy. Surgery is recommended in patients with functional impairment and metacarpophalangeal (MCP) joint contractures of 30° or more. There is no effective pharmacotherapy.

Adhesive capsulitis or “frozen shoulder” is treated with physiotherapy 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.¹
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 (eg, Potaba), although studies of oral therapies demonstrate inconsistent benefit. Intralausal injection therapy consisting of injection of interferon-\(\text{\textsuperscript{-2b}}\) or calcium channel-blockers (eg, verapamil) is the current standard of therapy.\(^2\) 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.

**Regulatory Status**

In February 2010, FDA approved Auxilium Pharmaceutical Inc.’s biologics license application for clostridial collagenase histolyticum (Xiaflex®) for treatment of adult patients with Dupuytren contracture with a palpable cord. FDA labeling for Xiaflex states that up to 3 injections at 4-week intervals may be given into a palpable Dupuytren cord with a contracture of a MCP joint or a proximal interphalangeal (PIP) joint.

In December 2013, FDA expanded the indications for Xiaflex to include Peyronie disease. Xiaflex is approved for men with a palpable penile plaque and penile curvature more than 30°. FDA labeling states that a treatment course consists of a maximum of 4 cycles, each of which consists of 2 Xiaflex injection procedures. In clinical trials of Xiaflex for Peyronie disease, corporeal rupture was reported as an adverse event in 0.5% of Xiaflex-treated patients. An additional 0.9% of Xiaflex-treated patients experienced a combination of penile ecchymosis or hematoma, sudden penile detumescence, and/or a penile “popping” sound or sensation, such that a diagnosis of corporal rupture could not be excluded. Severe penile hematoma was reported in 3.7% of patients. Because of these complications, FDA required a boxed warning label for Xiaflex as a treatment for Peyronie disease. Xiaflex is available for the treatment of Peyronie disease only through a restricted program under a Risk Evaluation and Mitigation Strategy (Xiaflex REMS Program). Required components of the REMS program are that prescribers are certified with the program by enrolling and completing training in the administration of Xiaflex for Peyronie disease and that healthcare sites are certified with the program and ensure that Xiaflex is only dispensed for use by certified prescribers.\(^3\)

**Rationale**

This policy was originally created in 2010 and was regularly updated with searches of the MEDLINE database. The most recent literature review covered the period through August 16, 2016. Following is a summary of the key findings to date.

**Dupuytren’s Disease (Dupuytren's Contracture)**

**Systematic Reviews**

Chen et al published a systematic review in 2011 of various treatments for Dupuytren contracture.\(^4\) Studies published through December 2010 were examined and included 4 prospective studies (including 2 randomized studies) on collagenase injections, 6 studies on open partial fasciotomy (including 2 randomized studies), and 3 studies on needle aponeurotomy. Sample sizes for all of the 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 of 50% to 58% (mean follow-up, 3-5 years), which were significantly higher than the open partial fasciectomy recurrence rates of 12% to 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 7727 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%). Pooled estimates and statistical comparisons are not reported.

Randomized Controlled Trials
This review identified 5 publications from 3 unique double-blind randomized controlled trials (RCTs) (including 2 follow-up RCT extension studies), all sponsored by the manufacturer (Auxilium Pharmaceuticals Inc.).

In 2009, Hurst et al published results from the Collagenase Option for Reduction of Dupuytren’s I study (CORD I), 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. Joints were stratified according to type (metacarpophalangeal [MCP] joints or proximal interphalangeal joint [PIP]) and severity of contracture and 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 1 day after injection if necessary. The primary end point was reduction in contracture to 0° to 5° of full extension 30 days after last injection. Twenty-six secondary end points 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 end point 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 end point 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 end point 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 end point.

When analyzed by joint type, more collagenase-treated joints achieved the primary end point than placebo (MCP, 76.7% vs 7.2%; proximal PIP joint, 40.9% vs 5.9%, both respectively) (p<0.001 for both comparisons). The 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 1 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 note 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. 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 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 comment that successful treatment of Dupuytren disease correlates with the percentage of excised Dupuytren tissue and the extent of the intervention. They caution 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. 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, 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 (eg, 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 1 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 CORD 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. 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 (eg, pain and swelling at the injection site).

In 2007, Badalamente and Hurst reported on patients who participated in a double-blind phase 3 RCT comparing collagenase and placebo injections. 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 up for 24 months. Over the 24 months following 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 subsequently 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 2013, 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. 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. End points included rate of clinical success (reduction in contracture to 0°-5° of normal) and percentage of AEs. There was no significant difference in clinical success by age, diabetes status, or sex, with 63% of cases reaching the end point. In addition, there was no difference in complication rates among the subgroups, with peripheral edema, contusion, and injection-site hemorrhage being most common.

Nonrandomized Comparative Studies
Since the publication of the RCTs previously described, several smaller nonrandomized studies have compared clostridial collagenase to 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). 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, the mean posttreatment contracture, decrease in contracture from baseline, and increase in ROM from baseline at the MCP and PIP joints did not significantly differ. The mean posttreatment ROM at the MCP joint was significantly higher in the clostridial collagenase-treated patients (90.7° vs 83.3°, p=0.02), while the posttreatment range of motion at the PIP was higher in the fasciectomy-treated patients, although the difference did not reach statistical significance (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 United Kingdom center, Povlsen et al prospectively compared outcomes for patients with single-digit Dupuytren contraction who underwent open fasciectomy (n=10) or clostridial collagenase injection followed by manipulation (n=10). 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 (ie, days) after the procedure. Longer term follow-up is not reported.

Noncomparative Studies
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 2 concurrent open-label, single-arm studies (JOIN I and JOIN 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. 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 end point 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 (JOIN I) and 20 Australian/European sites (JOIN II). 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 JOIN I and JOIN II were pooled to evaluate clinical success by contracture severity, the MCP and PIP joints with lesser contracture severity (ie, ≤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.

The relatively short-term (9-month) follow-up period in these 2 JOIN studies limits the ability to make conclusions regarding long-term outcomes, including the likelihood of recurrence. Patients who achieved clinical success in these 2 JOIN studies had the option to enroll in a 5-year follow-up study, which also included patients from the 2 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). Of 1080 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.

Other smaller single-arm series are summarized in Table 1.
<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Follow-Up Period</th>
<th>Overview of Findings</th>
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<tbody>
<tr>
<td>Watt et al (2010)</td>
<td>23 (8 with long-term follow up)</td>
<td>8 y</td>
<td>• In patients with isolated MCP contracture (N=6), 4 experienced recurrence by 8 y.</td>
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<td>• In patients with isolated PIP contracture (N=2), both experienced recurrence by 8 y</td>
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<td>Alberton et al (2013)</td>
<td>40 (32 with MCP, 8 with PIP contracture)</td>
<td>6 mo</td>
<td>• Clinical success occurred in 30 patients (75%)</td>
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<td>• AEs occurred in 23 patients (57.5%), 6 (15%) with ≥2 reactions. AEs included:</td>
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<td>o Skin tears (n=9)</td>
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<td>o Local hematoma (n=9)</td>
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<td>o Lymphangitis (n=3)</td>
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<td>o Blisters or epidermal necrosis (n=4)</td>
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<td>o Persistent edema with extension to fingers (n=2)</td>
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<td>Warwick et al (2014)</td>
<td>254</td>
<td>6 mo</td>
<td>• At follow-up, 87% of patients and 86% of physicians were very satisfied or satisfied with treatment</td>
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<td>• Treatment-related AEs occurred in 88% of patients, most commonly peripheral edema (44%), extremity pain (26%), and injection site pain (21%)</td>
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<td>Verheyden (2014)</td>
<td>144</td>
<td>Mean 35 d for patients with pretendinous cords; 38 d for patients with spiral cords</td>
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<td>• Demonstrated the feasibility of a novel technique; patients were treated with the entire bottle of enzyme, 0.78 mg, along with use of a novel slow intracord multicord injection</td>
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<td>• % achieving complete correction:</td>
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<td>o For MCP pretendinous cords: 83%</td>
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<td>o For PIP spiral cords: 58%</td>
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<td>• AEs:</td>
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<td>o All patients developed swelling, pain, and ecchymosis at the injection site</td>
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<td>o 35 skin lacerations were noted</td>
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<td>McMahon et al (2013)</td>
<td>102 treated (48 with follow-up available)</td>
<td>15 mo</td>
<td>• After cord rupture, contracture decreased from 48° (±21°) to 7 (±11°) in 64 joints treated</td>
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<td>• At latest follow-up, mean contracture was 15° (±19°)</td>
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<td>Recurrence rates:</td>
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<td>o 11/46 (24%) of MCP joints</td>
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Of 27 joints treated, 74.1% had ≥51% reduction of the original extension deficit.

Recurrence rates:
- Of 18 MCP joints treated, recurrence to ≥50° occurred on 0%, but recurrence to 5°-50° occurred in 33.3%.
- Of 9 PIP joints treated, recurrence to ≥40° occurred in 18.5% and to 5°-40° occurred in 7.4%.

Most patients (93.8%) experienced local AEs (e.g., ecchymosis, skin laceration, injection-site swelling, or hemorrhage).

**Section Summary**
The most direct evidence related to the use of clostridial collagenase for Dupuytren contractures comes from several RCTs, which compare clostridial collagenase to placebo injections, and generally show high rates of contracture resolution. This evidence is supported by nonrandomized comparative studies comparing clostridial collagenase to surgery, the largest of which, with 46 patients, reported similar outcomes with faster return-to-work and return-to-usual activities rates with clostridial collagenase. Rates of local AEs, including local swelling, pain, and ecchymosis, are generally high.

**Peyronie's Disease**

**Systematic Reviews**
In 2007, Russell et al conducted a systematic review of plaque injection therapy for Peyronie disease, which included 2 studies of collagenase.23 Both papers reported positive treatment outcomes. One study was rated, according to the Oxford Centre for Evidence-Based Medicine criteria as level 2 (RCT with low power or <80% follow-up/retention or good-quality, randomized prospective cohort study) and the other level 4 (case series or poor-quality cohort or case-control study). These 2 studies (published in 1985 and 1993) are noted next.24,25 Agents used in the other 19 studies reviewed were corticosteroid, verapamil, and interferon.

**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.25 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.26 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 the 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 versus 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.26

The development and validation of the PDQ was described by Hellstrom et al in 2013.27 Investigators developed the PDQ to quantitatively assess the symptoms and psychosexual consequences of Peyronie disease by provided 3 subscale domain scores, including psychological/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.

**Noncomparative Studies**

Several case series report outcomes from the treatment of clostridial collagenase for Peyronie disease. In a 1985 paper on a series of 31 men treated, 20 showed improvement.24 Pain was eliminated in 13 of 14 patients who experienced pain before treatment. One small corporeal rupture at the injection site was reported in 1 patient. No significant AEs were reported in 9.8 months of follow-up.

In 2008, Jordan reported on a series of 25 patients with well-defined plaque treated with 3 intralesional injections of clostridial collagenase over 7 to 10 days with repeat treatment at 3 months.28 Primary end points were changes from baseline in deviation angle and plaque size. Significant decreases from baseline were achieved in the mean deviation angle at months 3 (p<0.001) and 6 (p=0.001), plaque width at months 3 (p=0.005), 6 (p=0.024), and 9 (p=0.048), and plaque length at months 3 (p=0.002), and 6 (p=0.048). More than 50% of patients in this series considered themselves "very much improved" or "much improved" at all time-points in the study, and the drug was generally well-tolerated.

**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 their Peyronie disease. However, it is not clear that these improvements in curvature or in the degree of symptom bother translated to 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**

The following studies on injectable clostridial collagenase injections for fibroproliferative disorders were identified in a search of online site ClinicalTrials.gov in September 2014.

**Dupuytren Contractures**

- Injectable Collagenase and Percutaneous Needle Fasciotomy for Dupuytren's Contracture (NCT01538017): This is a randomized, open-label trial to compare clostridial collagenase with percutaneous needle fasciotomy in patients with Dupuytren contraction. Enrollment is planned for 50 subjects; the estimated study completion date is January 2015.
- Phase 2a Dose-ranging Study to Evaluate Safety and Effectiveness of AA4500 in Treatment of Dupuytren’s Disease Nodules (NCT02193828): This is a double-blinded RCT to compare the safety and efficacy of clostridial collagenase with placebo in the treatment of Dupuytren disease with at least 1 palmar nodule in the affected hand. Enrollment is planned for 90 subjects; the estimated study completion date is February 2015.

**Adhesive Capsulitis**

- A Phase 2a, Open-label, Dose-ranging Study of the Safety and Effectiveness of AA4500 for the Treatment of Adhesive Capsulitis of the Shoulder (NCT01483963): This is a randomized, unblinded trial to evaluate clostridial collagenase in the treatment of shoulder adhesive capsulitis. Enrollment was planned for 50 subjects. The study is listed as completed, but no results have been published.

- Clinical Study for the Treatment of Adhesive Capsulitis of the Shoulder (AC) (NCT02006719): This is a double-blinded RCT to compare clostridial collagenase with placebo in the treatment of adhesive capsulitis. The primary outcome is the change (degrees) from baseline to the day 95 follow-up in active forward flexion in the affected shoulder. Enrollment is planned for 300 subjects; the estimated study completion date is January 2015.

**Clinical Input Received through 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.

**2010 Input**

In response to requests, input was received from 2 physician specialty societies and 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’s contracture, comments were made about the limited amount of data on long-term outcomes and durability.

**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’s contracture noting lack of long-term data and head-to-head trials comparing collagenase to surgical options. However, despite considering this treatment investigational due to insufficient long-term evidence of effectiveness, 1 reviewer noted injectable clostridial collagenase for Dupuytren’s contracture is FDA approved and there is evidence of short-to-medium term effectiveness available. Five reviewers indicated injectable clostridial collagenase for Dupuytren’s 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’s contracture.

Four reviewers agreed injectable clostridium collagenase is investigational for the treatment of Peyronie’s Disease. One of these reviewers also commented that while this treatment is considered investigational, it may be indicated for Peyronie’s disease when it is bothersome noting 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.
Summary of Evidence

For patients with Dupuytren contracture, 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. Potentially serious adverse events also warrant further investigation, and evidence on long-term recurrence rates is limited. While gaps in the evidence base remain, this may be an appropriate treatment option in adult patients with a palpable cord based on short-term evidence of effectiveness and a preponderance of agreement from clinical input. Therefore, injectable clostridial collagenase may be considered medically necessary as an alternative to surgical options.

For other disorders, there is less evidence. Five studies, including 2 manufacturer-sponsored double-blind, placebo-controlled randomized trials, have demonstrated short-term improvement in penile curvature and self-reported distress from Peyronie-related symptoms in patients with Peyronie disease. However, evidence demonstrating health outcome improvements is lacking, as are comparisons with current treatments. Clostridial collagenase treatment for Peyronie plaques is associated with relatively high rates of risk for significant local adverse effects. No published literature that addressed the treatment of adhesive capsulitis with clostridial collagenase was identified. Based on the available evidence and clinical input, injection of clostridial collagenase is considered investigational for all other treatment indications, including Peyronie disease and adhesive capsulitis.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

Ralph et al developed guidelines for the treatment of Peyronie disease in 2010.29 These guidelines indicate surgery is the treatment of choice, although conservative management is an appropriate option.

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”).30

U.S. Preventive Services Task Force Recommendations

Injectable clostridial collagenase is not a preventive service.

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:


Billing Coding/Physician Documentation Information

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Additional Policy Key Words
5.01.19

Policy Implementation/Update Information

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<th>Date</th>
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<td>New Policy Titled Injectable Clostridial Collagenase for Fibroproliferative Disorders</td>
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<tr>
<td>12/2011</td>
<td>Policy updated with literature review; reference numbers 3, 6 and 14 added. Policy statement changed to may be considered medically necessary for Dupuytren's contracture in adult patients with a palpable cord. All other indications remain investigational.</td>
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<td>Policy updated with literature review through September 11, 2013; reference numbers 3, 9-10, 14, and 19 added; no change in policy statements</td>
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<td>8/2015</td>
<td>Revised-addition of Peyronie’s Disease as a medically necessary indication</td>
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