

<b>5.01.19</b>	<b>Injectable Clostridial Collagenase for Fibroproliferative Disorders</b>		
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<b>Section:</b>	5.0 Prescription Drug	<b>Page:</b>	Page 1 of 18

### Policy Statement

Injectable clostridial collagenase for the treatment of Dupuytren contracture in adults with a palpable cord may be considered **medically necessary**, 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:

- Adhesive capsulitis
- Cellulite
- Flexor tendon adhesions of the hand
- Peyronie disease

### Policy Guidelines

#### Multiple Injections

For patients with Dupuytren contracture, physicians should treat no more than 2 joints per hand per treatment visit (this is consistent with U.S. Food and Drug Administration labeling).

#### Coding

There is a HCPCS code specific to this drug:

- **J0775**: Injection, collagenase, clostridium histolyticum, 0.01 mg

The following CPT codes are specific for the treatment for Dupuytren contracture:

- **20527**: Injection, enzyme (e.g., collagenase), palmar fascial cord (i.e., Dupuytren's contracture)
- **26341**: Manipulation, palmar fascial cord (i.e., Dupuytren's cord), post enzyme injection (e.g., collagenase), single cord

CPT instructs that the custom orthotic fabrication/application would be coded separately.

Prior to 2012, there was no specific CPT code for this injection. The injection was likely reported with CPT code 20550 – injection(s); single tendon sheath, or ligament, aponeurosis (e.g., plantar “fascia”). This code might also be used for this treatment in adhesive capsulitis.

For the use of this treatment for Peyronie disease, the American Urological Association ([http://www.auanet.org/guidelines/peyronies-disease-\(2015\)](http://www.auanet.org/guidelines/peyronies-disease-(2015))) has recommended use of the following CPT codes:

- **54200**: Injection procedure for Peyronie disease
- **54235**: Injection of corpora cavernosa with pharmacologic agent(s) (e.g., papaverine, phentolamine). This part of the service is to induce an erection so that the location of the clostridial collagenase injection can be determined
- **96372**: Therapeutic, prophylactic, or diagnostic injection (specify substance or drug); subcutaneous or intramuscular. If the penis does not detumesce, this code might also be reported for administration of a medication to pharmacologically detumesce the penis

## Description

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

## Related Policies

- N/A

## Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

## Regulatory Status

Table 1 lists indications for clostridial collagenase (Xiaflex®; Auxilium Pharmaceuticals [Norristown, PA]) that have been approved by the Food and Drug Administration.

**Table 1. FDA-Approved Indications for Clostridial Collagenase (Xiaflex®)**

Indication	Approved	Indications	Additional Information
Dupuytren contracture	2010	<ul style="list-style-type: none"> <li>• Adults with Dupuytren contracture with a palpable cord</li> <li>• Up to 3 injections at 4-wk intervals into a palpable Dupuytren cord with a contracture of a metacarpophalangeal or a proximal interphalangeal joint</li> </ul>	<ul style="list-style-type: none"> <li>• Approval accompanied by REMS</li> <li>• The manufacturer must:                             <ul style="list-style-type: none"> <li>◦ Evaluate and mitigate risks and serious adverse events</li> <li>◦ Instruct health care providers on procedure to inject Xiaflex and perform finger extension procedures</li> <li>◦ Inform patients of potential risks of treatment</li> </ul> </li> </ul>
	2014	Indication expanded: up to 2 joints in same hand may be treated during a treatment visit	
Peyronie disease	2013	<ul style="list-style-type: none"> <li>• Men with a palpable penile plaque and penile curvature &gt;30°</li> <li>• A maximum of 4 cycles, each of which consists of 2 Xiaflex injection procedures</li> </ul>	<ul style="list-style-type: none"> <li>• Approval accompanied by black box warning of corporal rupture and penile hematoma</li> <li>• Only available through a restricted program (Xiaflex REMS), due to risk of corporal rupture. REMS requirements:                             <ul style="list-style-type: none"> <li>◦ Prescribers must enroll and complete training in administration of Xiaflex for treatment of Peyronie disease</li> <li>◦ Health care sites must be certified with the program and ensure that only certified prescribers administer Xiaflex</li> </ul> </li> </ul>

Adapted from Food and Drug Administration (2018).<sup>3</sup>

FDA: Food and Drug Administration; REMS: Risk Evaluation and Mitigation Strategy.

## Rationale

### Background

#### 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.

#### Dupuytren Disease

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 prevalence of Dupuytren disease is estimated at 3% to 6% in the general population and increases with advancing age. The disease is more common in people with diabetes or thyroid disease and among men.<sup>1</sup>

#### Treatment

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

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.

#### Treatment

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 have demonstrated inconsistent benefit. Intralesional injection therapy consisting of injection of interferon- $\alpha$ -2b or calcium channel-blockers (e.g., verapamil) is the current standard of therapy.<sup>2</sup> Surgical procedures involve the excision of hardened tissue and skin graft, the removal or pinching (plication) of tissue opposite the plaque to reduce curvature (the Nesbit procedure), penile implant, or a combination of these.

#### Adhesive Capsulitis

The prevalence of adhesive capsulitis is estimated at 2% to 3% in the general population and increases with advancing age; additionally, adhesive capsulitis is more common in people with diabetes or thyroid disease and among women.<sup>1</sup>

#### Treatment

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.

#### Clostridial Collagenase

Injection with clostridial collagenase is intended to provide a nonoperative treatment option for fibroproliferative disorders. Clostridial collagenase histolyticum is an enzyme produced by the bacterium *Clostridium histolyticum*, which has the physiologic effect of breaking down collagen. It has been developed and marketed pharmacologically as a treatment for disorders associated with collagen overdevelopment.

**Literature Review**

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function—including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice. The following is a summary of the key findings to date.

**Dupuytren Disease (Dupuytren Contracture)****Clinical Context and Therapy Purpose**

The purpose of administering local clostridial collagenase injection(s) in patients who have Dupuytren contracture is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does the use of local clostridial collagenase injection(s) improve the net health outcome in those with Dupuytren contracture?

The following PICOTS were used to select literature to inform this review.

**Patients**

The relevant population of interest is individuals with Dupuytren contracture.

**Interventions**

The therapy being considered is a local injection of clostridial collagenase.

**Comparators**

The following therapies and practices are currently being used to treat Dupuytren contracture: observation and surgical therapy.

**Outcomes**

The general outcomes of interest are recurrence rates, improvements in functional outcomes and quality of life and treatment-related adverse events.

**Timing**

Short-term follow-up is up to 3 days after injections are administered; long-term follow-up to monitor for recurrence is over 1 to 5 years.

**Setting**

Clostridial collagenase injections are administered in an outpatient setting under local anesthetic.

### **Systematic Reviews**

Smeraglia et al (2016) reported on the results of a systematic review of studies assessing on clostridial collagenase injections for Dupuytren contracture.<sup>4</sup> Reviewers included 43 studies (total N=6795 patients) published from 2000 to 2015, with some overlap across studies in terms of patient populations. Mean follow-up was 15 months (range, 1-96 months). Eighteen studies reported on primary outcomes of clinical satisfaction of patients and residual contracture of less than 5°, and 9 studies reported on patient satisfaction. Reviewers noted that longer term follow-up studies were necessary given the increase in contracture recurrence and that most studies lacked patient-related outcomes.

Brazzelli et al (2015) reported on a health technology assessment that included a systematic review of clostridial collagenase use for the treatment of Dupuytren contracture.<sup>5</sup> Reviewers included 8 RCTs, 7 nonrandomized comparative studies, and 15 observational studies (total N=7657 patients) involving collagenase and/or surgical interventions in patients with a palpable Dupuytren cord. No head-to-head RCTs comparing clostridial collagenase with surgery were identified by meta-analysis. Of the 5 RCTs comparing collagenase with placebo, three were included in a meta-analysis. In pooled analysis, the proportion of all first, first metacarpophalangeal (MCP), and first proximal interphalangeal (PIP) joints achieving clinical success favored clostridial collagenase (relative risk, 10.21; 95% confidence interval [CI], 5.29 to 19.69;  $I^2=0%$ ; relative risk, 10.27; 95% CI, 4.88 to 21.65;  $I^2=0%$ ; relative risk, 6.90; 95% CI, 4.28 to 11.12;  $I^2=0%$ , respectively). However, rates of local adverse events were higher in clostridial collagenase-treated patients.

Chen et al (2011) published a systematic review assessing various treatments for Dupuytren contracture.<sup>6</sup> 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 ranged from 13 to 261 patients. Reviewers found recurrence rates for collagenase injections (mean follow-up, 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, 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. Reviewers concluded that further study would be 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.

Peimer et al (2015) summarized the safety and tolerability of clostridial collagenase and surgical treatment (fasciectomy) for Dupuytren contracture.<sup>7</sup> The safety of clostridial collagenase was based on 11 clinical trials (n=1082 patients), while the safety of fasciectomy was based on 48 European studies (n=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 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**

Five publications from 3 unique double-blind, RCTs (including 2 follow-up RCT extension studies) were identified, all sponsored by Xiaflex manufacturer Auxilium Pharmaceuticals.

Hurst et al (2009) 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 *Clostridium histolyticum* for Dupuytren contracture in 308 subjects with joint contractures of 20° or more.<sup>8</sup> This trial was included in the 2011 Chen review (previously described).<sup>6</sup> Joints were stratified by type (MCP joints or PIP joint) and severity of contracture;

they were randomized 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 a reduction in contracture to 0° to 5° of full extension 30 days after the 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. Efficacy results were based on 306 primary joints: 203 injected with collagenase and 103 injected with a placebo. In the collagenase-treated group, 130 (64%) of 203 cords met the primary end point vs 7 (6.8%) of 103 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 joint, 76.7% vs 7.2%; 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 the 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 the last injection, 84.7% of collagenase-injected joints vs 11.7% of placebo-injected joints showed clinical improvement. Results were better in MCP joints than in PIP joints for the collagenase group (94.0% vs 67.1%) than for the placebo group (11.6% vs 11.8%), all respectively. 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 ( $p \leq 0.02$ ) than patients who received a placebo injection. Most were mild or moderate in intensity; however, 20 patients in the collagenase group and two in the placebo group reported severe events. Three severe adverse events were considered treatment-related (a case of complex regional pain syndrome, 2 tendon ruptures), and both required surgery. The CORD I authors noted that trial timeframe was insufficient to assess recurrence.

Witthaut et al (2011) reported on range of motion (ROM) outcomes from the CORD I study.<sup>9</sup> 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 did not (4.0°).

In a letter to the editor in response to the publication of the trial, Holzer and Holzer (2009) commented that successful treatment of Dupuytren disease correlates with the percentage of excised Dupuytren tissue and the extent of the intervention.<sup>10</sup> They cautioned that the value of collagenase injection must be confirmed in a long-term follow-up study that focuses on the recurrence rate.

Gilpin et al (2010) published the results of the CORD II study.<sup>11</sup> In this trial, 66 patients were randomized to 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 an increase of contracture to  $\geq 20^\circ$ ) 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 events related to 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.

McGrouther et al (2014) reported on results from a post hoc subgroup analysis of the randomized and open-label phases of the 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, based on the British Society of Surgery of the Hand classification.<sup>12</sup> 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  $\geq 20^\circ$  in the presence of a palpable cord in joints that had previously had clinical success) occurred in 3.8% of joints treated. Fifty-five (94.8%) patients developed treatment-related adverse events, all of which were considered mild (e.g., pain and swelling at the injection site).

Badalamente and Hurst (2007) reported on patients who participated in a double-blind, phase 3 RCT comparing collagenase with placebo injections.<sup>13</sup> 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), one before 12 months, two at 12 months, and two at 24 months after treatment. Three of these patients underwent fasciectomy. The most common adverse events were local reactions to injections.

Raven et al (2014) published a subgroup analysis of data pooled from the previously described 3 RCTs (CORD I, CORD II, Badalamente and Hurst [2007]) of collagenase treatment of Dupuytren-related contractures.<sup>14</sup> This analysis included 271 patients with MCP (n=167) or PIP (n=104) joint contractures of 20° or more treated with collagenase injections. Subgroups included age, sex, and diabetes status. End points included the rate of clinical success (reduction in contracture to 0°-5° of normal) and the percentage of adverse events. 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 subgroups, with peripheral edema, contusion, and injection-site hemorrhage being the most common.

### **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.

Zhou et al (2015) compared outcomes for patients who underwent clostridial collagenase injection or limited fasciectomy for Dupuytren contracture at 7 centers in the Netherlands.<sup>15</sup> 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 6 to 12 weeks postprocedure, the residual contracture for affected MCP joints did not differ significantly between groups (13° for clostridial collagenase vs 6° 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.

In a small study from a single U.K. center, Povlsen et al (2014) prospectively assessed outcomes for patients with single-digit Dupuytren contraction who underwent open fasciectomy (n=10) or clostridial collagenase injection followed by manipulation (n=10).<sup>16</sup> 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.

Naam et al (2013) retrospectively assessed patients who had Dupuytren contracture affecting at least 1 joint with a palpable cord who underwent clostridial collagenase injections (n=25) or fasciectomy (n=21).<sup>17</sup> Some patients who received clostridial collagenase injections were enrolled in the JOINT I study, described below. Over an average follow-up of 32 months for

patients treated with clostridial collagenase and 39 months for those treated with fasciectomy, mean posttreatment contracture, decrease in contracture from baseline, and increase in ROM from baseline at the MCP and PIP joints did not differ significantly. 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 ROM at the PIP joint 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.

### **Noncomparative Studies**

Noncomparative studies are discussed 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 the Collagenase Option for Reduction of Dupuytren Long-Term Evaluation of Safety Study (CORDLESS) studies.

Gaston et al (2015) reported on the 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.<sup>18</sup> 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 postbaseline 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.

Witthaut et al (2013) published findings from 2 concurrent open-label, single-arm studies (JOINT I, JOINT II) designed to evaluate the efficacy and safety of collagenase injections, which were used to reduce the degree of contracture in patients with advanced Dupuytren contracture at 9 months of follow-up.<sup>19</sup> 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 (JOINT I) and 20 Australian/European (JOINT II) sites. Similar results were reported in both studies. Seventy-one percent ( $n=625$ ) of joints 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 collagenase injections per cord. More MCP than PIP joints achieved clinical success (70% and 37%, respectively) and 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 (MCP joint, 19%; PIP joint, 21%), and satisfaction 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.,  $\leq 50^\circ$  and  $\leq 40^\circ$ , respectively) showed better responses 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 in these 2 JOINT studies limits the ability to make conclusions on long-term outcomes, including the likelihood of recurrence. Patients who

achieved clinical success in the 2 JOINT studies had the option to enroll in a 5-year follow-up study, which also included patients from the 2 CORD studies previously reviewed.

Peimer et al (2013) published interim data after the third year of the 5-year follow-up to CORDLESS.<sup>20</sup> 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 period. Five-year follow-up from the CORDLESS registry was reported in 2015.<sup>21</sup> Recurrence was reported in 47% (291/623) of successfully treated joints.

Badalamente et al (2015) 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 and reported on outcomes for clostridial collagenase for PIP contractures.<sup>22</sup> 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 in 34% after the last injection. Clinical improvement occurred in 49% of joints after 1 injection and in 58% 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.

A number of other smaller single-arm studies have reported on sample sizes ranging from 23 to 254 patients, and generally shorter term follow-up ( $\approx$  6 to 15 months).<sup>23-29</sup> One study, by Watt et al (2010), reported on 23 patients, eight of whom had follow-up to 8 years.<sup>23</sup> Among those with isolated MCP contracture (n=6), four experienced recurrence by 8 years, while both patients with isolated PIP contracture experienced recurrence by 8 years.

### **Section Summary: Dupuytren Contracture**

The most direct evidence related to the use of clostridial collagenase for Dupuytren contractures comes from several RCTs that compared clostridial collagenase with placebo injections, and generally showed high rates of contracture resolution. This evidence is supported by nonrandomized comparative studies comparing clostridial collagenase to surgery. Some studies have reported 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 mild local adverse events, including local swelling, pain, and ecchymosis, are generally high. Serious adverse events associated with therapy can include tendon rupture/injury, regional pain syndrome, and finger deformity. Additionally, long-term recurrence rates have been reported (e.g., 47% at 5 years).

### **Peyronie Disease**

#### **Clinical Context and Therapy Purpose**

The purpose of administering local clostridial collagenase injection(s) in patients who have Peyronie disease is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does the use of local clostridial collagenase injection(s) improve the net health outcome in men with Peyronie disease?

The following PICOTS were used to select literature to inform this review.

#### **Patients**

The relevant population of interest is men with Peyronie disease.

#### **Interventions**

The therapy being considered is a local injection of clostridial collagenase.

**Comparators**

The following therapies and practices are currently being used to treat Peyronie disease: observation, oral medications, and other intralesional treatment (e.g., verapamil).

**Outcomes**

The general outcomes of interest are improvements in functional outcomes and quality of life (e.g., sexual function) and treatment-related adverse events (e.g., rupture, hematoma).

**Timing**

Injections are administered 1- to 3-day cycles at specific intervals over about 24 weeks depending on the degree of curvature, followed by manual modeling.

**Setting**

Clostridial collagenase injections are administered in an outpatient setting under local anesthetic.

**Systematic Reviews**

Carson et al (2015) reported on a pooled analysis of 6 clinical studies to evaluate safety outcomes for clostridial collagenase for Peyronie disease.<sup>30</sup> 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.

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

**Randomized Controlled Trials**

Gelbard et al (2013) published the results of 2 double-blind, placebo-controlled randomized trials, the Investigation for Maximal Peyronie's Reduction Efficacy and Safety Studies (IMPRESS) I and II, which examined the clinical efficacy and safety of collagenase injections in subjects with Peyronie disease.<sup>34</sup> These RCTs were sponsored by the manufacturer (Auxilium Pharmaceuticals), the findings of which were submitted to the Food and Drug Administration in support of their biologics license application. These 2 trials 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 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, as well as the change in the Peyronie's Disease Questionnaire (PDQ; developed by the manufacturer; see discussion in the Peyronie's Disease section on PDQ validation) symptoms bother score from baseline to 52 weeks. Data from the IMPRESS I and II studies were pooled. 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 in the injection group (each  $p < 0.001$ ). The mean change in the PDQ symptom bother domain score was significantly improved in the collagenase group (-2.8) compared with the placebo group (-1.8;  $p = 0.004$ ). The most frequently reported complications ( $\geq 45\%$ ) in the collagenase-treated group included penile ecchymosis, penile swelling, and penile pain. Six participants experienced treatment-related serious adverse events, including corporeal rupture (3 cases) and penile hematoma (3 cases). All corporeal ruptures and 1 hematoma were successfully repaired surgically. Of the other 2 penile hematomas, 1 case resolved successfully without intervention, and the other ended with aspiration.

Lipshultz et al (2015) reported post hoc subgroup analyses from the combined data from the IMPRESS I and II studies.<sup>35</sup> 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 the duration of illness, the degree of plaque calcification, and the International Index of Erectile Function (IIEF) severity score. Reductions in penile curvature deformity occurred in all groups, though the 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. PDQ symptom bother score 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, a generalization of this analysis is limited by its post hoc design and small subgroups.

The development and validation of the PDQ have been described by Hellstrom et al (2013) using data from IMPRESS I and II studies.<sup>36</sup> Investigators developed the PDQ to assess quantitatively 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 using baseline data for 679 (81% of the total 836 enrolled) patients in IMPRESS I and II who had been sexually active in the last 3 months. PDQ domain scores did not significantly differentiate between patients with different degrees of curvature abnormality. Coyne et al (2015) assessed the responsiveness of the PDQ to changes in Peyronie disease symptoms in men from the IMPRESS I and II trials.<sup>37</sup> 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 Peyronie disease outcomes after treatment with clostridial collagenase. Many series are small (e.g., ≈20 patients)<sup>38</sup> or from earlier treatment eras (e.g., 1985), which limit their utility. However, some larger studies provide data on adverse events after clostridial collagenase treatment for Peyronie disease.

Carson et al (2015), discussed above, reported serious and nonserious adverse events after clostridial collagenase for Peyronie disease in a pooled analysis of clostridial collagenase recipients from 6 trials (total N=1044 patients).<sup>30</sup> Of treated patients, 85.8% (n=896) reported at least 1 treatment-related adverse event, most frequently penile hematoma (>25% of patients). Nine (0.9%) patients 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 (2015) described outcomes for 238 subjects with Peyronie disease treated with clostridial collagenase who had both a penile curvature measurement and a PDQ response at baseline and at least 1 subsequent time point (of 347 total subjects treated).<sup>39</sup> The degree of penile curvature improved from baseline to week 36 (34.4%; 95% CI, 31.2% to 37.6%) as did PDQ symptom bother score (mean change, 3.3; 95% CI, 2.8 to 3.7). However, the lack of a comparison group and exclusion of a high proportion of subjects (missing follow-up data) limit conclusions that can be drawn.

### **Section Summary: Peyronie Disease**

The most direct evidence on 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 translate into differences in patient outcomes or whether the benefit of treatment exceeds the risks.

### **Adhesive Capsulitis**

No studies assessing patients with adhesive capsulitis were identified in the literature search.

### **Summary of Evidence**

For individuals who have Dupuytren contracture who receive local clostridial collagenase injection(s), the evidence 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 has suggested 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 have reported similar outcomes with faster return-to-work and return-to-usual activities rates with clostridial collagenase, but 1 study reported poorer contraction improvement though lower adverse event rates. Evidence on long-term recurrence rates is somewhat limited, but 3- and 5-year follow-up from a large registry reported high recurrence rates (47% at 5 years). Although clostridial collagenase offers the potential benefit of 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.

For individuals who have Peyronie disease who receive local clostridial collagenase injection(s), the evidence 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 reductions in self-reported distress from symptoms related to Peyronie disease. However, evidence demonstrating improvements in health outcome is lacking, as are studies comparing clostridial collagenase with other therapies for Peyronie disease. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have adhesive capsulitis who receive local clostridial collagenase injection(s), the evidence is very limited. Relevant outcomes are symptoms, change in disease status, functional outcomes, and quality of life. No published literature addressing the treatment of adhesive capsulitis with clostridial collagenase was identified. The evidence is insufficient to determine the effects of the technology on health outcomes.

### **Supplemental Information**

#### **Clinical Input 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 from Blue Cross Blue Shield Association, input was received from 2 physician specialty societies (2 reviews) and 5 academic medical centers (6 reviews) 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, another 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. Five reviewers indicated injectable clostridial collagenase for Dupuytren contracture might be considered

medically necessary; they noted it is a treatment alternative to surgery. This recommendation 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 from Blue Cross Blue Shield Association, input was received from 6 academic medical centers in 2010. Input was mixed, with half of those providing offering comments 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 Dupuytren Contracture**

#### ***National Institute for Health and Care Excellence***

The National Institute for Health and Care Excellence (2017) recommended the use of collagenase *Clostridium histolyticum* to treat adults with Dupuytren contracture in cases of moderate disease where percutaneous needle fasciotomy is not an option.<sup>40</sup> The Institute advised that the decision to use collagenase clostridium rather than limited fasciectomy should be made only after thorough discussion between the patient and caregiver; the Institute further defined appropriate outpatient treatment as consisting of a single injection at a time and administered by a qualified hand surgeon.

#### ***American Urological Association***

The American Urological Association (2015) issued guidelines on the diagnosis and treatment of Peyronie disease.<sup>41</sup> 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), the Association recommended intralesional collagenase *Clostridium histolyticum* in combination with modeling (moderate recommendation; evidence strength grade B).

#### ***European Association of Urology***

The European Association of Urology (2012) guidelines on penile curvature indicated 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").<sup>42</sup>

#### **Adhesive Capsulitis**

##### ***National Institute for Health Research***

The National Institute for Health Research (2012) published a health technology assessment on the management of adhesive capsulitis.<sup>43</sup> In this assessment, collagenase injections were not included in the treatments considered for adhesive capsulitis.

### **U.S. Preventive Services Task Force Recommendations**

Not applicable.

### **Medicare National Coverage**

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

### Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 2.

**Table 2. Summary of Key Trials**

NCT No.	Trial Name	Planned Enrollment	Completion Date
<b>Ongoing</b>			
NCT02301078	Comparing Short-term Function and Pain After Treatment With Collagenase Clostridium Histolyticum or Percutaneous Needle Aponeurotomy for Dupuytren's Disease	60	Nov 2017 (ongoing)
NCT02725528	A Multi-Center, Randomized Controlled Trial Comparing The Clinical Effectiveness and Cost-Effectiveness of Collagenase Injection (Xiaflex) and Palmar Fasciectomy in the Management of Dupuytren's Disease	128	Nov 2019
NCT03000114	Comparison of Collagenase Injection and Percutaneous Needle Aponeurotomy for Treatment of Dupuytren's Disease	334	Jan 2021
ISRCTN18254597	Dupuytren's interventions surgery vs collagenase	710	Oct 2021
<b>Unpublished</b>			
NCT02267460 <sup>a</sup>	A Phase 3b, 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	30	Mar 2016 (completed)
NCT01538017	Comparing Injectable Collagenase (CI) and Percutaneous Needle Fasciotomy (PNF) for Dupuytren's Contracture (DC) Affecting Proximal Interphalangeal Joints (PIP). A Randomised Controlled Trial	50	Nov 2015 (completed)
NCT02006719 <sup>a</sup>	A Randomized, Double-blind, Placebo-controlled Study of the Safety and Efficacy of AA4500 for the Treatment of Adhesive Capsulitis of the Shoulder	322	Dec 2014 (completed)
NCT02193828 <sup>a</sup>	A Phase 2a, Double-blind, Randomized, Placebo-Controlled, Dose-Ranging Study to Evaluate the Safety and Effectiveness of AA4500 in the Treatment of Dupuytren's Disease Nodules	76	Mar 2014 (completed)

ISRCTN: International Standard Randomised Controlled Trials Number; NCT: national clinical trial.

<sup>a</sup> Denotes industry-sponsored or cosponsored trial.

### References

1. Dias R, Cutts S, Massoud S. Frozen shoulder. *BMJ*. Dec 17 2005;331(7530):1453-1456. PMID 16356983
2. Hellstrom WJ. Medical management of Peyronie's disease. *J Androl*. Jul-Aug 2009;30(4):397-405. PMID 18974422
3. Food and Drug Administration (FDA). Xiaflex: collagenase clostridium histolyticum. 2018; [http://www.endo.com/File%20Library/Products/Prescribing%20Information/Xiaflex\\_prescribing\\_information.html#LINK\\_a7d1f7e8-79cf-49aa-8e76-3ddc035530db](http://www.endo.com/File%20Library/Products/Prescribing%20Information/Xiaflex_prescribing_information.html#LINK_a7d1f7e8-79cf-49aa-8e76-3ddc035530db). Accessed September 25, 2018.
4. Smeraglia F, Del Buono A, Maffulli N. Collagenase clostridium histolyticum in Dupuytren's contracture: a systematic review. *Br Med Bull*. Jun 2016;118(1):149-158. PMID 27151958
5. Brazzelli M, Cruickshank M, Tassie E, et al. Collagenase clostridium histolyticum for the treatment of Dupuytren's contracture: systematic review and economic evaluation. *Health Technol Assess*. Oct 2015;19(90):1-202. PMID 26524616
6. Chen NC, Srinivasan RC, Shauver MJ, et al. A systematic review of outcomes of fasciotomy, aponeurotomy, and collagenase treatments for Dupuytren's contracture. *Hand (N Y)*. Sep 2011;6(3):250-255. PMID 22942847
7. Peimer CA, Wilbrand S, Gerber RA, et al. Safety and tolerability of collagenase Clostridium histolyticum and fasciectomy for Dupuytren's contracture. *J Hand Surg Eur Vol*. Feb 2015;40(2):141-149. PMID 24698851

8. Hurst LC, Badalamente MA, Hentz VR, et al. Injectable collagenase clostridium histolyticum for Dupuytren's contracture. *N Engl J Med*. Sep 3 2009;361(10):968-979. PMID 19726771
9. Witthaut J, Bushmakin AG, Gerber RA, et al. Determining clinically important changes in range of motion in patients with Dupuytren's Contracture: secondary analysis of the randomized, double-blind, placebo-controlled CORD I study. *Clin Drug Investig*. Nov 1 2011;31(11):791-798. PMID 21967070
10. Holzer LA, Holzer G. Injectable collagenase clostridium histolyticum for Dupuytren's contracture. *N Engl J Med*. Dec 24 2009;361(26):2579; author reply 2579-2580. PMID 20050321
11. Gilpin D, Coleman S, Hall S, et al. Injectable collagenase Clostridium histolyticum: a new nonsurgical treatment for Dupuytren's disease. *J Hand Surg Am*. Dec 2010;35(12):2027-2038 e2021. PMID 21134613
12. McGrouther DA, Jenkins A, Brown S, et al. The efficacy and safety of collagenase clostridium histolyticum in the treatment of patients with moderate Dupuytren's contracture. *Curr Med Res Opin*. Apr 2014;30(4):733-739. PMID 24397625
13. Badalamente MA, Hurst LC. Efficacy and safety of injectable mixed collagenase subtypes in the treatment of Dupuytren's contracture. *J Hand Surg Am*. Jul-Aug 2007;32(6):767-774. PMID 17606053
14. Raven RB, 3rd, Kushner H, Nguyen D, et al. Analysis of efficacy and safety of treatment with collagenase Clostridium histolyticum among subgroups of patients with Dupuytren contracture. *Ann Plast Surg*. Sep 2014;73(3):286-290. PMID 23511746
15. Zhou C, Hovius SE, Slijper HP, et al. Collagenase Clostridium histolyticum versus limited fasciectomy for Dupuytren's contracture: outcomes from a multicenter propensity score matched study. *Plast Reconstr Surg*. Jul 2015;136(1):87-97. PMID 25829153
16. Povlsen B, Povlsen SD. What is the better treatment for single digit Dupuytren's contracture: surgical release or collagenase clostridium histolyticum (Xiapex) injection? *Hand Surg*. Aug 25 2014:1-4. PMID 25155703
17. Naam NH. Functional outcome of collagenase injections compared with fasciectomy in treatment of Dupuytren's contracture. *Hand (N Y)*. Dec 2013;8(4):410-416. PMID 24426958
18. Gaston RG, Larsen SE, Pess GM, et al. Efficacy and safety of concurrent collagenase clostridium histolyticum injections for 2 Dupuytren contractures in the same hand: a prospective, multicenter study. *J Hand Surg*. Oct 2015;40(10):1963-1971. PMID 26216077
19. Witthaut J, Jones G, Skrepnik N, et al. Efficacy and safety of collagenase clostridium histolyticum injection for Dupuytren contracture: short-term results from 2 open-label studies. *J Hand Surg Am*. Jan 2013;38(1):2-11. PMID 23218556
20. Peimer CA, Blazar P, Coleman S, et al. Dupuytren contracture recurrence following treatment with collagenase clostridium histolyticum (CORDLESS study): 3-year data. *J Hand Surg Am*. Jan 2013;38(1):12-22. PMID 23200951
21. Peimer CA, Blazar P, Coleman S, et al. Dupuytren contracture recurrence following treatment with Collagenase Clostridium histolyticum (CORDLESS [Collagenase Option for Reduction of Dupuytren Long-Term Evaluation of Safety Study]): 5-Year Data. *J Hand Surg*. Aug 2015;40(8):1597-1605. PMID 26096221
22. Badalamente MA, Hurst LC, Benhaim P, et al. Efficacy and safety of collagenase clostridium histolyticum in the treatment of proximal interphalangeal joints in Dupuytren contracture: combined analysis of 4 phase 3 clinical trials. *J Hand Surg*. May 2015;40(5):975-983. PMID 25843533
23. Watt AJ, Curtin CM, Hentz VR. Collagenase injection as nonsurgical treatment of Dupuytren's disease: 8-year follow-up. *J Hand Surg Am*. Apr 2010;35(4):534-539, 539 e531. PMID 20353858
24. Alberton F, Corain M, Garofano A, et al. Efficacy and safety of collagenase Clostridium histolyticum injection for Dupuytren contracture: report of 40 cases. *Musculoskelet Surg*. Dec 2014;98(3):225-232. PMID 24254968
25. Warwick D, Arner M, Pajardi G, et al. Collagenase clostridium histolyticum in patients with Dupuytren's contracture: results from POINT X, an open-label study of clinical and patient-reported outcomes. *J Hand Surg Eur Vol*. Feb 2015;40(2):124-132. PMID 24470559

26. Verheyden JR. Early outcomes of a sequential series of 144 patients with Dupuytren's contracture treated by collagenase injection using an increased dose, multi-cord technique. *J Hand Surg Eur Vol.* Feb 2015;40(2):133-140. PMID 24698852
27. McMahon HA, Bachoura A, Jacoby SM, et al. Examining the efficacy and maintenance of contracture correction after collagenase clostridium histolyticum treatment for Dupuytren's disease. *Hand (N Y).* Sep 2013;8(3):261-266. PMID 24426932
28. Sood A, Therattil PJ, Paik AM, et al. Treatment of Dupuytren disease with injectable collagenase in a veteran population: a case series at the department of veterans affairs new jersey health care system. *Eplasty.* Apr 2014;14:e13. PMID 24741384
29. Atroshi I, Nordenskjold J, Lauritzson A, et al. Collagenase treatment of Dupuytren's contracture using a modified injection method: a prospective cohort study of skin tears in 164 hands, including short-term outcome. *Acta Orthop.* Jun 2015;86(3):310-315. PMID 25695745
30. Carson CC, 3rd, Sadeghi-Nejad H, Tursi JP, et al. Analysis of the clinical safety of intralesional injection of collagenase Clostridium histolyticum (CCH) for adults with Peyronie's disease (PD). *BJU Int.* Nov 2015;116(5):815-822. PMID 25818264
31. Russell S, Steers W, McVary KT. Systematic evidence-based analysis of plaque injection therapy for Peyronie's disease. *Eur Urol.* Mar 2007;51(3):640-647. PMID 17092631
32. Gelbard MK, Lindner A, Kaufman JJ. The use of collagenase in the treatment of Peyronie's disease. *J Urol.* Aug 1985;134(2):280-283. PMID 2991611
33. Gelbard MK, James K, Riach P, et al. Collagenase versus placebo in the treatment of Peyronie's disease: a double-blind study. *J Urol.* Jan 1993;149(1):56-58. PMID 8417217
34. Gelbard M, Goldstein I, Hellstrom WJ, et al. Clinical efficacy, safety and tolerability of collagenase clostridium histolyticum for the treatment of Peyronie disease in 2 large double-blind, randomized, placebo controlled phase 3 studies. *J Urol.* Jul 2013;190(1):199-207. PMID 23376148
35. Lipshultz LI, Goldstein I, Seftel AD, et al. Clinical efficacy of collagenase Clostridium histolyticum in the treatment of Peyronie's disease by subgroup: results from two large, double-blind, randomized, placebo-controlled, phase III studies. *BJU Int.* Oct 2015;116(4):650-656. PMID 25711400
36. Hellstrom WJ, Feldman R, Rosen RC, et al. Bother and distress associated with Peyronie's disease: validation of the Peyronie's disease questionnaire. *J Urol.* Aug 2013;190(2):627-634. PMID 23376705
37. Coyne KS, Currie BM, Thompson CL, et al. Responsiveness of the Peyronie's Disease Questionnaire (PDQ). *J Sex Med.* Apr 2015;12(4):1072-1079. PMID 25664497
38. Jordan GH. The use of intralesional clostridial collagenase injection therapy for Peyronie's disease: a prospective, single-center, non-placebo-controlled study. *J Sex Med.* Jan 2008;5(1):180-187. PMID 18173766
39. Levine LA, Cuzin B, Mark S, et al. Clinical safety and effectiveness of collagenase clostridium histolyticum injection in patients with Peyronie's disease: a phase 3 open-label study. *J Sex Med.* Jan 2015;12(1):248-258. PMID 25388099
40. National Institute for Health and Care Excellence (NICE). Collagenase clostridium histolyticum for treating Dupuytren's contracture [TA459]. 2017; <https://www.nice.org.uk/guidance/TA459/chapter/1-Recommendations>. Accessed September 25, 2018.
41. Nehra A, Alterowitz R, Culkin DJ, et al. Peyronie's Disease: AUA Guideline. 2015; [http://www.auanet.org/guidelines/peyronies-disease-\(2015\)](http://www.auanet.org/guidelines/peyronies-disease-(2015)). Accessed November 29, 2017.
42. Hatzimouratidis K, Eardley I, Giuliano F, et al. EAU guidelines on penile curvatures. *Eur Urol.* Sep 2012;62(3):543-552. PMID 22658761
43. Maund E, Craig D, Suekarran S, et al. Management of frozen shoulder: a systematic review and cost-effectiveness analysis. *Health Technol Assess.* Mar 2012;16(11):1-264. PMID 22405512
44. Blue Cross Blue Shield Association. Medical Policy Reference Manual, No. 5.01.19 (October 2018).

## Documentation for Clinical Review

Please provide the following documentation (if/when requested):

Procedure report(s) or progress note(s)

- History and physical and/or consultation notes including:
  - Identification of finger joint being treated
  - Previous injection dates (if applicable)
  - Treatment plan (e.g., planned injections)

**Post Service**

- Procedure report(s) or progress note(s)

## Coding

*This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of codes does not constitute or imply member coverage or provider reimbursement.*

**MN/IE**

The following services may be considered medically necessary in certain instances and investigational in others. Services may be considered medically necessary when policy criteria are met. Services may be considered investigational when the policy criteria are not met or when the code describes application of a product in the position statement that is investigational.

Type	Code	Description
CPT®	20527	Injection, enzyme (e.g., collagenase), palmar fascial cord (i.e., Dupuytren's contracture)
	20550	Injection(s); single tendon sheath, or ligament, aponeurosis (e.g., plantar "fascia")
	26341	Manipulation, palmar fascial cord (i.e., Dupuytren's cord), post enzyme injection (e.g., collagenase), single cord
	54200	Injection procedure for Peyronie disease
	54235	Injection of corpora cavernosa with pharmacologic agent(s) (e.g., papaverine, phentolamine)
	96372	Therapeutic, prophylactic, or diagnostic injection (specify substance or drug); subcutaneous or intramuscular
HCPCS	J0775	Injection, collagenase, clostridium histolyticum, 0.01 mg
ICD-10 Procedure	3E0U33Z	Introduction of Anti-inflammatory into Joints, Percutaneous Approach

## Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action	Reason
07/06/2012	New policy	Medical Policy Committee
07/31/2015	Coding update	Administrative Review
01/01/2016	Policy title change from Collagenase Clostridium Histolyticum Injections Policy revision without position change	Medical Policy Committee
11/01/2016	Policy revision without position change	Medical Policy Committee

Effective Date	Action	Reason
12/01/2017	Policy revision without position change	Medical Policy Committee
02/01/2018	Policy revision without position change	Medical Policy Committee
12/01/2018	Policy revision without position change	Medical Policy Committee

### Definitions of Decision Determinations

**Medically Necessary:** A treatment, procedure, or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.

**Investigational/Experimental:** A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

**Split Evaluation:** Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

### Prior Authorization Requirements (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department. Please call (800) 541-6652 or visit the provider portal at [www.blueshieldca.com/provider](http://www.blueshieldca.com/provider).

*Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.*