Injectable Clostridial Collagenase for Fibroproliferative Disorders

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Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Dupuytren's Contracture

Based on review of available data, the Company considers the use of injectable clostridial collagenase (Xiaflex®)‡ for Dupuytren's contracture with palpable cord, to be **eligible for coverage.****

Patient Selection Criteria

Coverage eligibility for the use of injectable clostridial collagenase (Xiaflex) will be considered when ALL of the following criteria are met:

- Patient has a diagnosis of Dupuytren's contracture with palpable cord; AND
- Patient is 18 years of age or older; AND
- The requested dose will not exceed three 0.58 mg injections per cord at approximately 4-week intervals; AND
- No more than two cords in the same hand will be injected per treatment visit.

Peyronie's Disease

Based on review of available data, the Company considers the use of injectable clostridial collagenase (Xiaflex) for Peyronie's disease to be **eligible for coverage.****

Patient Selection Criteria

Coverage eligibility for the use of one course of injectable clostridial collagenase (Xiaflex) per palpable plaque will be considered when ALL of the following criteria are met:

- Patient is 18 years of age or older; AND
- Patient has a diagnosis of Peyronie's disease with a palpable plaque; AND
- Patient has a curvature deformity of at least 30 degrees at the start of therapy; AND

- Xiaflex will be used in combination with a penile modeling procedure; AND
- The requested dose will not exceed 0.58 mg into the targeted plaque once on each of 2 days for no more than 4 treatment cycles.
  NOTE: Each treatment cycle may be repeated at approximately 6-week intervals.

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of injectable clostridial collagenase (Xiaflex) when patient selection criteria are not met OR for other uses including, but not limited to adhesive capsulitis to be i**nvestigational**.*

Background/Overview

Collagenases are enzymes that digest native collagen and are being evaluated for treatment of fibroproliferative disorders such as Dupuytren's contracture and Peyronie's disease. Clostridial collagenase is a bacterial collagenase derived from *Clostridium histolyticum*. Treatment of Dupuytren's contracture consists of injection of collagenase into the cord followed by manipulation of the finger if contracture persists. Injection may be done up to 3 times at 4-week intervals. Treatment with Xiaflex for Peyronie's disease in indicated in patients with a palpable plaque and curvature deformity of at least 30 degrees at the start of therapy. A treatment cycle consists of two Xiaflex injection procedures and a penile modeling procedure. The penile modeling procedure involves manipulations of the flaccid penis to stretch and elongate the treated plaque. Both hands should be used to apply firm, steady pressure to elongate and stretch the plaque. The goal is to gradually create bending opposite to the patient's penile curvature, with stretching to the point of moderate resistance. Pressure should be held for 30 seconds and then released. Allow a 30 second rest period, and repeat the modeling procedure for a total of 3 modeling attempts at 30 seconds each. Patients should also perform penile modeling at home at least 3 times daily for 30 seconds. For each plaque causing the curvature deformity, up to four treatment cycles may be administered. Each cycle can be repeated at 6 week intervals therefore making each course approximately 24 weeks.

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

The mechanisms that contribute to the pathology are poorly understood. In Dupuytren's 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's 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 (MCP)-joint contractures of 30 degrees 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's disease and adhesive capsulitis is estimated at 3–6% and 2–3%, respectively, in the general population and increases with advancing age. Both conditions are more common in patients with diabetes or thyroid disease. Dupuytren's disease is more common in men, and adhesive capsulitis more common in women.

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

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

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

In December 2013, the FDA approved Xiaflex for the treatment of adult men with Peyronie's Disease with a palpable plaque and curvature deformity of at least 30 degrees at the start of therapy. A treatment cycle consists of two Xiaflex injection procedures and a penile modeling procedure. For each plaque causing the curvature deformity, up to four treatment cycles may be administered. Each cycle can be repeated at 6 week intervals.

Centers for Medicare and Medicaid Services (CMS)

There is no national coverage determination.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to regulations, other plan medical policies, and accredited national guidelines.

A number of nonsurgical interventions for fibroproliferative disease have been studied. Investigations of a potential role for injectable clostridial collagenase have been ongoing over a period of 20 years. The FDA approval was granted in 2010 for treatment of Dupuytren's contracture with a palpable cord. FDA approval for Peyronie's disease was granted in 2013.

Dupuytren's Disease (Dupuytren's Contracture)

Clostridial collagenase has been compared with percutaneous needle fasciotomy in 4 RCTs in individuals with Dupuytren's contracture. All the RCTs were conducted outside of the United States. Three RCTs were single-center and the fourth was a 2-center RCT. The RCTs were heterogenous in the types of joints involved and in the definitions of treatment success and recurrence. All the trials used similar treatment protocols, and 3 of the 4 trials explicitly included study participants with a palpable cord. After 2 to 3 years follow-up, there were no statistically significant differences between treatment groups for any outcome measure, suggesting that clostridial collagenase and surgery provide similar long-term benefits. It is notable that recurrence commonly occurred in both treatment groups. The studies had some methodological limitations, most notably not reporting outcome clinical significance a priori and lack of blinding.

Clostridial collagenase has been compared to surgery other than percutaneous needle fasciotomy in 3 small, mostly short-term nonrandomized studies (N=132). Compared with surgery, findings from these studies suggest that clostridial collagenase may provide similar benefits and fewer adverse events at least in the short-term. However, their small sample sizes, lack of long-term follow-up, and limited data on the most clinically meaningful outcomes preclude reaching strong conclusions based on their findings.

In individuals with Dupuytren's contracture, for the comparison of collagenase injection to placebo and for long-term outcomes, the best available evidence comes from systematic reviews by Smeraglia et al (2016) and Brazzelli et al (2015). The review by Smeraglia and colleagues includes the largest number of studies to-date, but it did not include any quantitative analyses. Therefore, quantitative findings from the next largest and most recent review by Brazzelli and colleagues are also provided. Both reviews included the 3 placebo-controlled RCTs sponsored by Xiaflex manufacturer Auxilium Pharmaceuticals. The reviews also included numerous nonrandomized comparative studies and noncomparative studies to address gaps in the RCTs for recurrence rates.

The reviews rated the RCTs as having low risk of important biases. Limitations included lack of blinding of outcome assessors. The RCTs were also industry sponsored. The Dupuytren's contracture selection criteria used in the RCTs included that participants have 1 cord, contracture between 20° and 100° for the metacarpophalangeal joint, and contracture between 20° and 80° for the proximal interphalangeal joint. Mean baseline contracture for the metacarpophalangeal and proximal interphalangeal joints ranged from 44° to 51° and from 43° to 53°, respectively.

In the RCTs, the clinically meaningful outcome was 'clinical success', which was defined as a reduction in contracture to 0 to 5° of normal, within 30 days after the last injection. Pooled analyses from the review by Brazzelli and colleagues found greater rates of clinical success for clostridial collagenase (63%; range, 44% to 91%) compared with placebo (6%; range, 0% to 7%), which was a statistically significant difference. The clinical success advantage for clostridial collagenase compared to placebo was greater for the metacarpophalangeal joints (relative risk [RR], 10.27; 95% confidence interval [CI], 4.88 to 21.65; n = 254) compared to the proximal interphalangeal joints (RR, 7.44; 95% CI, 2.44 to 22.62; n = 153)

Adverse events were significantly more frequent for participants receiving clostridial collagenase compared with placebo. In the RCTs, the proportions of participants experiencing at least 1 adverse event were 97% in the clostridial collagenase groups (range, 97% to 100%) and 28% in the placebo groups (range, 21% to 75%). Peripheral edema was the most frequent adverse event reported, which occurred in 73% of participants receiving clostridial collagenase compared with 5% in the placebo groups. The next most common mild and local adverse events included contusion, pain in extremity, and injection site pain. Serious adverse events were rare and not evaluated in a meta-analysis. Only 1.5% of participants who received clostridial collagenase (4/272) experienced a serious adverse event, including 1 case of complex regional pain syndrome and 2 cases of tendon rupture in CORD I and 1 case of flexion pulley rupture in CORD II.

In the systematic review by Smeraglia and colleagues, recurrence was typically defined as a decrease in passive extension that exceeded 20° and was reported in 12 studies (N=2401). This included data from the RCTs with follow-up that ranged from 3 to 24 months, as well as from an additional 9 nonrandomized studies with follow-up that extended to 88 months. Neither review performed meta-analyses on this outcome, but both reviews observed that recurrence rates tended to increase over time. Recurrence rates ranged from 0% to 4% in studies with follow-up from 3 to 12 months, from 0% to 28% in studies with follow-up of 15 to 24 months, and from 36% to 75% in studies with follow-up from 36 to 88 months. However, authors of the review by Smeraglia and colleagues and the nonrandomized, surgery-controlled study by Nydick et al (2013) have raised questions about the clinical relevance of defining recurrence as a decrease in passive extension that exceeded 20°. For example, authors of Nydick et al (2013) pointed out that although the recurrence rate of 75% is high in the longest-term, a very small case series by Watt et al (2010) noted, "none of these patients had further intervention on the injected finger." Further, authors of the review by Smeraglia and colleagues proposed that a more clinically relevant definition of recurrence may be contracture

greater than 30°, as this is the threshold for which surgery is indicated. In the Collagenase Option for Reduction of Dupuytren Long-Term Evaluation of Safety Study (CORDLESS) study, using the threshold of contracture greater than 30° led to a lower rate of 5-year recurrence of 32%.

For functional outcomes, relevant findings were identified from only 1 open-label, single-arm study reported by Naam and colleagues in 2013. This study retrospectively assessed patients who had Dupuytren's contracture affecting at least 1 joint with a palpable cord who underwent clostridial collagenase injections (n=25) or fasciectomy (n=21). 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 range of motion from baseline at the metacarpophalangeal and proximal interphalangeal joints did not differ significantly. Mean posttreatment range of motion at the metacarpophalangeal 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 proximal interphalangeal 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.

No study has yet reported any quality of life outcomes.

Peyronie's Disease

In 2022, Cao and colleagues conducted a systematic review and meta-analysis of 5 RCTs comparing clostridial collagenase with placebo, including the Investigation for Maximal Peyronie's Reduction Efficacy and Safety Studies (IMPRESS) I and II studies, described below. The review included evidence from 1227 individuals (mean age, 57 years), including 815 who received clostridial collagenase and 412 who received placebo. Pooled results favored clostridial collagenase over placebo for penile curvature deformity (weighted mean difference [WMD], -18.77; 95% CI, -22.58 to -14.96; I2 = 38%) and Peyronie's Disease Symptom Bother (WMD, -1.20; 95% CI, -1.69 to -0.72; I2 = 0%). The review found no statistically significant difference between clostridial collagenase and placebo (WMD, -0.64; 95% CI, -2.09 to 0.81) and heterogeneity was high (I2 = 67%). Treatment-related adverse events were more likely to occur with clostridial collagenase compared with placebo (OR, 12.86; 95% CI, 9.17 to 18.04; I2 = 0%). Specific event rates were also higher with clostridial collagenase than placebo, including penile pain (odds ratio [OR] 8.87; 95% CI, 5.43 to 14.50; I2 = 0%), edema (OR, 26.86; 95% CI, 6.63 to 108.0; I2 = 0%), injection site pain (OR, 7.91; 95% CI, 4.38 to 14.30; I2 = 0%), and contusion (OR, 14.60; 95% CI, 4.13 to 51.68; I2 = 0%) based on imprecise risk estimates. Study authors noted that while these results appear promising, confirmatory RCT evidence with larger sample sizes is needed.

A 2023 Cochrane review of non-surgical therapies for Peyronie's Disease included only one publication (Gelbard et al [2013]), which is summarized below, for outcomes associated with collagenase injections in this population.

In 2013, Gelbard and colleagues 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's disease. These RCTs were sponsored by the manufacturer (Auxilium Pharmaceuticals), the findings of which were submitted to the 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 degrees) 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 to 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 $p < 0.0001$). The mean change in the PDQ symptom bother domain score was significantly improved in the collagenase group vs. the placebo group (-2.8 ± 3.8 vs. -1.8 ± 3.5, $p=0.0037$). 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 in 3 cases and penile hematoma in the other 3 cases. The 3 corporeal ruptures and one hematoma were successfully repaired surgically. Of the 2 remaining penile hematomas, one case was successfully resolved without intervention and the other resolved with aspiration.

In 2015, Lipshultz and colleagues reported post hoc subgroup analyses from combined data from the IMPRESS I and II studies. This analysis included a modified intention-to-treat population of 612 subjects who had a penile curvature deformity measurement, 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. Investigators developed the PDQ to assess quantitatively the symptoms and psychosexual consequences of Peyronie's disease by 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's disease symptoms in men from the IMPRESS I and II trials. In this group, PDQ psychological and physical symptoms and symptom bother subscales significantly discriminated patient improvement in responses to a global assessment of the PDQ and degree of penile curvature at weeks 24 and 52.

Case series have reported Peyronie's disease outcomes after treatment with clostridial collagenase. Many series are small (e.g., ~20 patients) 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's disease.

Goldstein et al (2020) reported noncomparative 5-year outcomes in men treated with clostridial collagenase. The study included 280 men previously enrolled in the IMPRESS I and II trials or in the AUX-CC 802 or 806 open-label studies. After a mean 4.6 years of follow-up, in 180 men with data, there was a 9.1% improvement in mean penile curvature relative to their final measure in their original study enrollment. Mean PDQ bother (N = 123; p = 0.0003), psychological and physical symptoms (N = 119; p = 0.0004), and pain (N = 52; p= 0.04) were all significantly improved compared with the last measure of their previous study. Serious adverse events occurred in 2.1% (6/280) of the population. Due to the high number of participants with missing follow-up data (27%) and the lack of a comparison group, these study results should be interpreted with caution.

A single-arm, open-label trial reported by Levine et al (2015) described outcomes for 238 subjects with Peyronie's 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). 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.

Adhesive Capsulitis

Evidence on the use of clostridial collagenase for the treatment of adhesive capsulitis is extremely limited. Fitzpatrick et al (2020) reported results from 11 participants enrolled at a single center comparing clostridial collagenase injection (n = 9) with placebo (n = 2). There was no statistically significant difference between clostridial collagenase and placebo in shoulder function based on measures of range of motion after 3 months of follow up. Adverse events that included bruising and swelling occurred in 100% (9/9) of participants receiving clostridial collagenase injection and no (0/2) placebo participants. These results are part of a larger randomized trial of 322 participants at 46 sites which was completed in 2014. Complete results for the trial remain unpublished although Fitzpatrick et al note that their findings were consistent with those of the full trial population.

Evidence on the use of clostridial collagenase for treatment of adhesive capsulitis is extremely limited. One small substudy of a larger, unpublished RCT found no benefit of clostridial collagenase injection over placebo in functional outcomes, with increased adverse events.

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.

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In response to requests, input was received from 2 physician specialty societies (2 reviews) and 5 academic medical centers (6 reviews). 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, one reviewer noted that 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 that 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
For individuals with Dupuytren's contracture who receive clostridial collagenase, the evidence includes systematic reviews, randomized controlled trials (RCTs), and nonrandomized comparative studies. Relevant outcomes are symptoms, change in disease status, functional outcomes, and quality of life. Findings from randomized and nonrandomized studies comparing clostridial collagenase to surgery suggest similar benefits and harms. However, limited data on the most clinically meaningful outcomes preclude reaching strong conclusions based on their findings. Findings from systematic reviews of randomized, placebo-controlled trials, nonrandomized controlled studies, and noncomparative studies consistently demonstrated clinically important benefits for clostridial collagenase. However, data on quality of life have not yet emerged. Rates of mild local adverse events, including local swelling, contusion and pain, are generally high, but serious adverse events have been rare. In comparative studies, the risk of contracture recurrence appears to increase over

time regardless of treatment group. However, as recurrence rates vary by the definition of recurrence (contracture greater than 20° or 30°, and/or when further intervention is needed), standardization of the definition is still needed. Although clostridial collagenase offers the potential benefit of less-invasive treatment for Dupuytren's contracture with clinically meaningful benefits and a low risk of major complications, important gaps in the evidence base exist related to treatment durability and impact on quality of life. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have Peyronie's disease who receive local clostridial collagenase injection(s), the evidence includes a systematic review, randomized trials, and numerous nonrandomized comparative 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's disease. However, evidence demonstrating improvements in health outcomes is lacking, as are studies comparing clostridial collagenase with other therapies for Peyronie's disease. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have adhesive capsulitis who receive local clostridial collagenase injection(s), evidence is lacking. Relevant outcomes are symptoms, change in disease status, functional outcomes, and quality of life. One small substudy of an RCT found no benefit of clostridial collagenase injection over placebo in functional outcomes, with increased adverse events. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For other disorders, there is less evidence. Therefore, based on available evidence and clinical input, injection of this agent is considered investigational for all other treatment indications.

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Policy History

Original Effective Date: 06/16/2010
Current Effective Date: 03/10/2025

06/03/2010	Medical Policy Committee approval
06/16/2010	Medical Policy Implementation Committee approval. New policy.
05/05/2011	Medical Policy Committee review
05/18/2011	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

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05/03/2012	Medical Policy Committee review
05/16/2012	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
05/02/2013	Medical Policy Committee review
05/22/2013	Medical Policy Implementation Committee approval. Added a Patient Selection Criteria section for coverage eligibility requiring that patients have a diagnosis of Dupuytren's contracture with palpable cord and are 18 years and older. Added that the use of injectable clostridial collagenase (Xiaflex) if Patient Selection Criteria are not met is investigational.
01/09/2014	Medical Policy Committee review
01/15/2014	Medical Policy Implementation Committee approval. Added new indication for Peyronie's disease and associated criteria. Updated background information and references.
01/08/2015	Medical Policy Committee review
01/21/2015	Medical Policy Implementation Committee approval. No change to coverage.
01/07/2016	Medical Policy Committee review
01/22/2016	Medical Policy Implementation Committee approval. No change to coverage.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
01/05/2017	Medical Policy Committee review
01/18/2017	Medical Policy Implementation Committee approval. No change to coverage.
01/04/2018	Medical Policy Committee review
01/17/2018	Medical Policy Implementation Committee approval. No change to coverage.
01/10/2019	Medical Policy Committee review
01/23/2019	Medical Policy Implementation Committee approval. No change to coverage.
01/03/2020	Medical Policy Committee review
01/08/2020	Medical Policy Implementation Committee approval. No change to coverage.
01/07/2021	Medical Policy Committee review
01/13/2021	Medical Policy Implementation Committee approval. No change to coverage.
01/06/2022	Medical Policy Committee review
01/12/2022	Medical Policy Implementation Committee approval. No change to coverage.
01/05/2023	Medical Policy Committee review
01/11/2023	Medical Policy Implementation Committee approval. No change to coverage.
01/04/2024	Medical Policy Committee review
01/10/2024	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
02/06/2025	Medical Policy Committee review
02/12/2025	Medical Policy Implementation Committee approval. Added FDA approved dosing to criteria. Updated literature review.

Next Scheduled Review Date: 02/2026

Injectable Clostridial Collagenase for Fibroproliferative Disorders

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Coding

The five character codes included in the Louisiana Blue Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2024 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	20527, 20550, 26341, 54200, 54235
HCPCS	J0775
ICD-10 Diagnosis	M72.0, M75.00-M75.02, N48.6

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or

B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

NOTICE: 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 eligibility for coverage.