I. POLICY

Injectable clostridial collagenase for the treatment of Dupuytren’s contracture in adult patients with a palpable cord may be considered medically necessary, for up to three injections at intervals of at least thirty days.

Injectable clostridial collagenase may be considered medically necessary 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.

Injectable clostridial collagenase is considered investigational for all other indications including, but not limited to adhesive capsulitis. There is insufficient evidence to support a conclusion concerning the health outcomes or benefits associated with this procedure.

II. PRODUCT VARIATIONS

[N] = No product variation, policy applies as stated
[Y] = Standard product coverage varies from application of this policy, see below

[N] Capital Cares 4 Kids
[N] Indemnity
[N] PPO
[N] SpecialCare
[N] HMO
[N] POS
[N] SeniorBlue HMO
[N] FEP PPO*
[N] SeniorBlue PPO

*Refer to FEP Medical Policy Manual MP-10.12.02, Xiaflex. The FEP Medical Policy Manual can be found at: www.fepblue.org

III. DESCRIPTION/BACKGROUND

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.

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 results in nodules and cords in the palm and fingers resulting 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. 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. Intraleisional 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.

Regulatory Status
In February 2010, the U.S. Food and Drug Administration (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 metacarpophalangeal (MCP) joint or a proximal interphalangeal (PIP) joint.

On December 6, 2013, Xiaflex was FDA-approved for treatment of adult men with Peyronie’s disease. A treatment cycle consists of two Xiaflex injection procedure and a penile modeling procedure. For each plaque causing the curvature deformity, up to four treatment cycles may be administered. Each treatment cycle may be repeated at approximately six-week intervals. If the curvature deformity is less than 15 degrees after the first, second, or third treatment cycle, or if further treatment is not clinically indicated, then subsequent treatment cycles should not be administered.

IV. RATIONALE

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. FDA approval was granted in 2010 for treatment of Dupuytren’s contracture with a palpable cord. Some authors include collagenase among standard injection therapies for Peyronie’s disease.

Dupuytren’s Disease (Dupuytren’s Contracture)

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

In 2009, Hurst and colleagues published results from CORD I, a randomized, double-blind placebo-controlled, multicenter trial (16 sites) of collagenase clostridium histolyticum for Dupuytren’s contracture with 308 subjects with joint contractures of 20 degrees or more. (4) This
study was included in the Chen review described above. (3) Joints were stratified according to type (metacarpophalangeal [MCP] joints or proximal interphalangeal joint [PIP]) and severity of contracture and randomly assigned in a 2:1 ratio to receive up to 3 injections of either collagenase or placebo in the contracted collagen cord at 30-day intervals. Secondary and tertiary joints were identified for possible subsequent injections. Joints were manipulated one day after injection if necessary. The primary endpoint was reduction in contracture to 0–5 degrees of full extension 30 days after last injection. Twenty-six secondary endpoints were also evaluated.

Recurrence of contracture was defined as an increase in joint contracture equal to or greater than 20 degrees and was considered an adverse event. Efficacy results were based on 306 primary joints: 203 injected with collagenase and 103 injected with placebo. In the collagenase-treated group, 130 of 203 (64%) cords met the primary endpoint versus 7 of 103 (6.8%) placebo-injected cords (p<0.001). More than half of the collagenase-injected joints that did not meet the primary endpoint did not receive the maximum allowable number of injections, most commonly because a cord could not be palpated or the patient was satisfied with the result. Median time to reach the primary endpoint for collagenase-treated primary joints was 56 days. At the 90-day visit, there was no recurrence of contracture in collagenase-treated primary joints that had reached the primary endpoint.

When analyzed by joint type, more collagenase-treated joints achieved the primary endpoint than placebo (MCP 76.7% vs. 7.2% and proximal PIP joint 40.9% vs. 5.9%, both respectively) (p<0.001 for both comparisons). The mean change in contracture from baseline to 30 days after last injection was 48.0 to 7.2 degrees in the collagen-injected MCP joints and 45.4 to 43.1 degrees in the placebo-injected MCP joints. Thirty days after last injection, 84.7% of collagenase-injected joints versus 11.7% of placebo-injected joints showed clinical improvement. Results were better in MCP joints than in PIP joints: 94.0% versus 67.1%, respectively, in the collagenase group and 11.6% versus 11.8%, respectively, in the placebo group. Overall, 96.6% of patients who received collagenase reported at least one treatment-related adverse event. They had significantly more injection- and manipulation-related events, such as contusion, hemorrhage, injection-site pain, upper extremity pain, and lymphadenopathy (p ≤0.02), than patients who received placebo injection. Most were mild or moderate in intensity; however, 20 patients in the collagenase group and 2 in the placebo group reported events that were severe in intensity. Three severe adverse events were considered to be treatment-related: a case of complex regional pain syndrome and 2 tendon ruptures, both requiring surgical procedures. The CORD I authors note that the timeframe of this study was insufficient to assess recurrence, and they could not make any claims about this outcome. In 2011, Witthaut and colleagues reported on range of motion (ROM) outcomes from the CORD I study. (5) On day 30, mean ROM increased from 43.9 degrees to 80.7 degrees in joints treated with collagenase. In the joints treated with placebo, mean ROM increased 45.3 degrees to 49.5 degrees on day 30. Using regression models to create a ROM severity classification, the authors reported joints treated
with collagenase had a significant mean increase in ROM of 36.7 degrees (p <0.001) whereas, joints treated with placebo had a non-significant mean increase of 4.0 degrees.

In a letter to the editor in response to publication of the study, Holzer and Holzer comment that successful treatment of Dupuytren’s disease correlates with the percentage of excised Dupuytren’s tissue and the extent of the intervention. (6) They caution that the value of collagenase injection must be confirmed in a long-term follow-up study that focuses on the recurrence rate.

In 2010, Gilpin and colleagues published results of the CORD II study. (7) In this study, 66 patients were randomized to receive collagenase injection (45 cords) or placebo (21 cords) in the 90-day, double-blind phase followed by an open label phase of 9 months. The authors reported, within 30 days, collagenase injections resulted in significantly more cord contracture improvement from baseline to within 0-5 degrees of normal than placebo (44.4% vs. 4.8%, respectively). Results after the open-label treatment were reported to be similar to the double-blind phase. Recurrence of contracture (defined as increase of contracture to 20 degrees or more) did not occur during the 12-month follow-up. All study participants experienced mild adverse events (e.g., swelling and pain at injection site). Three serious adverse effects related to the treatment were reported. A flexion pulley rupture of the left small finger occurred in one patient while rapid thickening of the treated cord and sensory abnormalities occurred in another patient.

Watt and colleagues, in 2010, reported on a Phase II clinical trial of 23 patients 8 of whom completed 8-years follow-up. (8) In the isolated MCP group (n=6), average contracture was 57 degrees before treatment, 9 degrees at 1 week, 11 degrees at 1 year, and 23 degrees at 8-year follow-up. Four of 6 patients experienced recurrence by the 8-year follow-up. In the isolated PIP joint group (n=2), both patients had recurrence by 8-year follow-up. Outcomes at specific intervals between 1 year and 8 years were not reported. Potential bias in patient selection and the small number of patients precludes drawing conclusions from this report.

In a 2010 review, Desai and Hentz make several observations regarding the role of collagenase in the treatment of Dupuytren’s contracture. (9) They recommend caution when treating the small finger; all 3 tendon ruptures seen across all studies reported to the U.S. Food and Drug Administration (FDA) and adverse events of boutonniere deformity and pulley injury occurred in the small finger. An active immune response was seen in patients after injection of collagen in the clinical trials, which suggests the possibility that effectiveness of subsequent injections might be impacted. The authors also note that long-term effects of repeat injections and contracture recurrence have yet to be studied, and direct comparisons with the current gold standard, palmar fasciectomy, have not been made.
In 2007, Badalamente and Hurst reported on patients who participated in a double-blind Phase III randomized controlled trial (RCT) comparing collagenase and placebo injections. (10) During the double-blind and open-label phases, 62 joints (31 MCP and 31 PIP) were treated in 35 patients. Fifty-four (87%) were clinical successes. Twenty-seven joints were followed up for 24 months. Over the 24 months following the last injection, 5 joints had recurrences (1 MCP and 4 PIP), 1 before 12 months, 2 at 12 months, and 2 at 24 months after treatment. Three of these patients subsequently underwent fasciectomy. The most common adverse events were local reactions to injections. The limited patient follow-up makes it difficult to reach conclusions from this study.

**Peyronie’s Disease**

Authors of a 2007 systematic review of plaque injection therapy included 2 studies of collagenase in their analysis. (11) Both papers reported positive treatment outcomes. One study was rated, according to the Oxford Centre for Evidence-Based Medicine criteria, as level 2 (RCT with low power or <80% follow-up/retention or good-quality, randomized prospective cohort study) and the other level 4 (case series or poor-quality cohort or case-control study). These 2 studies are noted below. (12, 13) Agents used in the other 19 studies reviewed were corticosteroid, verapamil, and interferon. In a 1985 paper on a series of 31 men treated, 20 showed improvement. (12) Pain was eliminated in 13 of 14 patients who experienced pain before treatment. One small corporeal rupture at the injection site was reported in one patient. No significant adverse events were reported in 9.8 months of follow-up. In a 1993 randomized, placebo-controlled, double-blind study with 49 subjects reported by the same author, the effects of collagenase and placebo on plaque size and penile deformity were investigated. For the group as a whole, treatment with collagenase was significantly more effective (p<0.007). Patients with lesser deformity responded more favorably to treatment. (13) In 2008, Jordan reported on a series of 25 patients with well-defined plaque treated with 3 intralesional injections of clostridial collagenase over 7–10 days with repeat treatment at 3 months. (14) Primary endpoints were changes from baseline in deviation angle and plaque size. Significant decreases from baseline were achieved in the mean deviation angle at months 3 (p=0.0001) and 6 (p=0.0012), plaque width at months 3 (p=0.0052), 6 (p=0.0239), and 9 (p=0.0484), and plaque length at months 3 (p=0.0018) and 6 (p=0.0483). More than 50% of patients in this series considered themselves "very much improved" or "much improved" at all time points in the study, and the drug was generally well-tolerated.
Adhesive Capsulitis

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

Ongoing Clinical Trials

Several studies on injectable clostridial collagenase injections for Dupuytren’s contractures were identified in a search of online site ClinicalTrials.gov in August 2012. In a randomized study of 50 patients, collagenase injections will be compared to percutaneous needle fasciotomy (NCT01538017) for Dupuytren’s contracture. In the CORDLESS observational study (Collagenase Optimal Reduction of Dupuytren's - Long-term Evaluation of Success Study), the long-term durability and safety of clostridial collagenase injections for Dupuytren’s contracture will be evaluated yearly in 600 patients (NCT00954746). In a Phase IV, randomized trial, the effects of delayed manipulation of digits following collagenase injections for the treatment of Dupuytren’s contracture will be examined in 60 patients (NCT01226121). Outcomes after collagenase injection for Dupuytren’s contracture will be studied in a Phase III study of 250 patients followed for 11 months (NCT01229436). The safety and efficacy of 2 injections of clostridial collagenase into the same hand of 60 patients with multiple Dupuytren’s contractures will be evaluated in a Phase III study. (NCT01407068). Retreatment with collagenase injections for recurrent Dupuytren’s contracture will be evaluated in a non-randomized study of 100 patients (NCT01498640).

Injectable collagenase will be evaluated in a randomized study of 50 subjects for adhesive capsulitis of the shoulder (NCT01483963).

Clinical Input Received through Physician Specialty Societies and Academic Medical Centers

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

2010

In response to requests, input was received from no physician specialty societies and 6 academic medical centers while this policy was under review in 2010. The input was mixed, with half those providing input agreeing that use of this agent is investigational. While there was support for use in Dupuytren’s contracture, comments were made about the limited amount of data on long-term outcomes and durability.
2011

In response to requests, input was received from 2 physician specialty societies (2 reviews) and 5 academic medical centers (6 reviews) while this policy was under review in 2011. Two reviewers indicated injectable clostridium collagenase is investigational for the treatment of Dupuytren’s contracture noting lack of long-term data and head-to-head trials comparing collagenase to surgical options. However, despite considering this treatment investigational due to insufficient long-term evidence of effectiveness, 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 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.

2014

Peyronie’s Disease
The efficacy of XIAFLEX was evaluated in two randomized, double-blind, placebo-controlled, multi-centered trials in 832 adult males with Peyronie’s disease (Studies 1 and 2). At study entry, patients must have had penile curvature deformity of at least 30 degrees in the stable phase of Peyronie’s disease. Patients were excluded if they had a ventral curvature deformity, an isolated hourglass deformity or a calcified plaque that could have interfered with the injection technique. At baseline, penile pain was either not present or was mild in most (98%) patients. In these trials, patients were given up to 4 treatment cycles of XIAFLEX or placebo (weeks 0, 6, 12, 18), and were followed in a non-treatment follow-up period (weeks 24-52). In each treatment cycle, two injections of XIAFLEX or two injections of placebo were administered 1 to 3 days apart. A penile modeling procedure was performed on patients at the study site 1 to 3 days after the second injection of the cycle. The treatment cycle was repeated at approximately six-week intervals for up to three additional times, for a maximum of 8 total injection procedures and 4 total modeling procedures. In addition, patients were instructed to perform penile modeling at home for six weeks after each treatment cycle [see Medication Guide].

Table 8 shows the baseline disease characteristics of patients with Peyronie’s disease in Studies 1 and 2.
Table 8. Baseline Disease Characteristics of Patientsa with Peyronie’s Disease (PD)

<table>
<thead>
<tr>
<th>Study 1</th>
<th></th>
<th>Study 2</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>XIAFLEX</td>
<td>Placebo</td>
<td>XIAFLEX</td>
</tr>
<tr>
<td>N=277</td>
<td>N=140</td>
<td>N=274</td>
<td>N=141</td>
</tr>
<tr>
<td>Mean age (years) (Min-Max)</td>
<td>57.9 (28 - 79)</td>
<td>58.2 (30 - 81)</td>
<td>57.3 (23 - 84)</td>
</tr>
<tr>
<td>Mean duration of PD (years) (Min-Max)</td>
<td>3.9 (1.0 - 35.9)</td>
<td>4.8 (1.0 - 50.8)</td>
<td>4.2 (1.1 - 30.9)</td>
</tr>
<tr>
<td>Mean Penile Curvature Deformity (degrees) (Min-Max)</td>
<td>48.8 (30-90)</td>
<td>49.0 (30-89)</td>
<td>51.3 (30-90)</td>
</tr>
<tr>
<td>Peyronie’s Disease Questionnaire (PDQ)b – Mean Patient-Reported PD Bother Domain Score (range: 0-16) c</td>
<td>7.5</td>
<td>7.4</td>
<td>7.4</td>
</tr>
<tr>
<td>History of Erectile Dysfunction N (%)</td>
<td>128 (46.2)</td>
<td>75 (53.6)</td>
<td>134 (48.9)</td>
</tr>
</tbody>
</table>

a Subjects were from ITT population and received at least one dose of study drug in Study 1 or 2
b Each PDQ assessment required subjects to have had vaginal intercourse in the 3 months prior to completion
c Higher scores represent worse symptoms

Before the first dose of study drug was administered, eligible subjects were stratified by the degree of curvature deformity (30 to 60 degrees, and 61 to 90 degrees) and then randomized into two treatment groups to receive either XIAFLEX or placebo in a 2:1 ratio. The efficacy population (modified intent-to-treat (mITT) population) comprised a total of 612 intent-to-treat subjects who had both a curvature deformity measurement and a PDQ assessment at baseline, and at one or more subsequent time points in Studies 1 and 2, and had engaged in vaginal intercourse within 3 months prior to each PDQ assessment.

In Studies 1 and 2, the co-primary endpoints were:

• the percent change from baseline to Week 52 in penile curvature deformity and;
• the change from baseline to Week 52 in the Bother domain score of the PDQ

The Bother domain score is a composite of the following patient-reported items: concern about erection pain, erection appearance, and the impact of Peyronie’s disease on intercourse and on frequency of intercourse.

[Note: Final page is signature page and is kept on file, but not issued with Policy.]
Penile curvature deformity (co-primary endpoint)

XIAFLEX treatment significantly improved penile curvature deformity in patients with Peyronie’s disease compared with placebo (see Table 9). The improvement in curvature deformity was numerically similar among subjects with baseline curvature deformity from 30 to 60 degrees and those with curvature deformity from 61 to 90 degrees.

Table 9. Mean Percent Change in Penile Curvature Deformity from Baseline to Week 52 – Studies 1 and 2

<table>
<thead>
<tr>
<th></th>
<th>Study 1</th>
<th>Study 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>XIAFLEX N=199</td>
<td>XIAFLEX N=202</td>
</tr>
<tr>
<td>Baseline Mean (degrees)</td>
<td>48.8°</td>
<td>51.3°</td>
</tr>
<tr>
<td>Mean Percent Change*</td>
<td>-35.0%</td>
<td>-17.8%</td>
</tr>
<tr>
<td>Treatment Difference (95% CI)</td>
<td>-17.8% - 6.6%</td>
<td>-11.4% - 3.3%</td>
</tr>
</tbody>
</table>
| * Mean percent change, treatment difference, 95% CI, and p-value were based on an ANOVA model with factors for treatment, stratum of baseline penile curvature, and their interaction and using last observation carried forward (LOCF) in the modified intent-to-treat (mITT) population. The mITT population was defined as all randomized subjects who had both a penile curvature deformity measurement and a PDQ assessment at baseline and at one or more subsequent time points.
| b p-value < 0.01 |

Figure 1. Mean Percent Change in Penile Curvature Deformity – Study 1

ANOVA model -adjusted values with factors for treatment, stratum of baseline penile curvature, and their interaction and using last observation carried forward (LOCF) in the modified intent-to-treat (mITT) population.
Peyronie’s Disease Questionnaire Bother domain score (co-primary endpoint)

XIAFLEX significantly reduced patient-reported bother associated with Peyronie’s disease compared with placebo (see Table 10). The reduction in the bother domain score was numerically similar between patient groups stratified by degree of baseline curvature deformity (30 to 60 degrees, and 61 to 90 degrees).

Table 10. Mean Change in Peyronie’s Disease Bother Domain Score from Baseline to Week 52 – Studies 1 and 2

<table>
<thead>
<tr>
<th></th>
<th>Study 1</th>
<th>Study 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>XIAFLEX</td>
<td>Placebo</td>
</tr>
<tr>
<td>Baseline Mean</td>
<td>7.5</td>
<td>7.4</td>
</tr>
<tr>
<td>Mean Change</td>
<td>-2.8</td>
<td>-1.6</td>
</tr>
<tr>
<td>Treatment Difference (95% CI)</td>
<td>(-2.4, -0.03)</td>
<td>(-2.1, -0.002)</td>
</tr>
</tbody>
</table>

\(^{a}\) Mean change, treatment difference, 95% CI, and p-value all based on an ANOVA model with factors for treatment, stratum of baseline penile curvature, and their interaction and using last observation carried forward (LOCF) in the modified intent-to-treat (mITT) population. The mITT population was defined as all randomized subjects who had both a penile curvature deformity measurement and a PDQ assessment at baseline and at one or more subsequent time points.

\(^{b}\) p-value < 0.05.

Figure 2. Mean Percent Change in Penile Curvature Deformity – Study 2

ANOVA model - adjusted values with factors for treatment, stratum of baseline penile curvature, and their interaction and using last observation carried forward (LOCF) in the modified intent-to-treat (mITT) population.
**MEDICAL POLICY**

**POLICY TITLE**
INJECTABLE CLOSTRIDIAL COLLAGENASE FOR FIBROPROLIFERATIVE DISORDERS (XIAFLEX®)

**POLICY NUMBER**
MP-2.153

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**Figure 3. Mean Change in Patient-Reported Peyronie’s Disease Bother Domain Score – Study 1**

ANOVA model–adjusted values with factors for treatment, stratum of baseline penile curvature, and their interaction and using last observation carried forward (LOCF) in the modified intent-to-treat (mITT) population.

**Figure 4. Mean Change in Patient-Reported Peyronie’s Disease Bother Domain Score – Study 2**

ANOVA model–adjusted values with factors for treatment, stratum of baseline penile curvature, and their interaction and using last observation carried forward (LOCF) in the modified intent-to-treat (mITT) population.

[Note: Final page is signature page and is kept on file, but not issued with Policy.]
There were no clinically meaningful differences in the mean percent improvement in curvature deformity or mean reduction in the bother domain score following treatment with XIAFLEX based on the severity of baseline erectile dysfunction or concomitant phosphodiesterase type 5 (PDE5) inhibitor use.

Summary

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.

For patients with Dupuytren’s contracture, the evidence from clinical trials suggests that injectable clostridial collagenase provides short-term release of contracture. A comparison of overall outcomes compared to surgical intervention may be useful; however, studies with direct comparisons are not available. Potentially serious adverse events also warrant further investigation, and evidence on long-term recurrence rates is limited. While gaps in the evidence base remain, this may be an appropriate treatment option in adult patients with a palpable cord based on short-term evidence of effectiveness and a preponderance of agreement from clinical input. Therefore, injectable clostridial collagenase may be considered medically necessary as an alternative to surgical options.

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

Practice Guidelines and Position Statements

Ralph and colleagues developed guidelines for the treatment of Peyronie’s disease in 2010. (15) These guidelines indicate surgery is the treatment of choice, although conservative management is an appropriate option.

The 2012 European Association of Urology (EAU) guidelines on penile curvature indicate injectable collagenase is a treatment option for Peyronie’s 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”). (16)
V. DEFINITIONS

ADHESIVE CAPSULITIS- Adherence of folds causing inflammatory thickening in an articular (joint) capsule, esp. the shoulder, thereby restricting movement.

VI. BENEFIT VARIATIONS

The existence of this medical policy does not mean that this service is a covered benefit under the member’s contract. Benefit determinations should be based in all cases on the applicable contract language. Medical policies do not constitute a description of benefits. A member’s individual or group customer benefits govern which services are covered, which are excluded, and which are subject to benefit limits and which require preauthorization. Members and providers should consult the member’s benefit information or contact Capital for benefit information.

VII. DISCLAIMER

Capital’s medical policies are developed to assist in administering a member’s benefits, do not constitute medical advice and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical policy and a member’s benefit information, the benefit information will govern. Capital considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.

VIII. REFERENCES


Other:
Taber’s Cyclopedic Medical Dictionary 20th edition.

IX. CODING INFORMATION

Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

Covered when Medically Necessary as outlined in policy section above:

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<thead>
<tr>
<th>CPT Codes®</th>
<th>Description</th>
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<td></td>
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<td>26341</td>
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<table>
<thead>
<tr>
<th>HCPCS Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>C9266</td>
<td>INJECTION, COLLAGENASE CLOSTRIDIUM HISTOLYTICUM, 0.1 MG</td>
</tr>
<tr>
<td>J0775</td>
<td>INJECTION, COLLAGENASE, CLOSTRIDIUM HISTOLYTICUM, 0.01 MG</td>
</tr>
</tbody>
</table>
MEDICAL POLICY

POLICY TITLE
INJECTABLE CLOSTRIDIAL COLLAGENASE FOR
FIBROPROLIFERATIVE DISORDERS (XIAFLEX®)

POLICY NUMBER
MP-2.153

<table>
<thead>
<tr>
<th>ICD-9-CM Diagnosis Code*</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>607.85</td>
<td>Peyronie's disease</td>
</tr>
<tr>
<td>728.6</td>
<td>Contracture of palmar fascia</td>
</tr>
</tbody>
</table>

*If applicable, please see Medicare LCD or NCD for additional covered diagnoses.

The following ICD-10 diagnosis codes will be effective October 1, 2015:

<table>
<thead>
<tr>
<th>ICD-10-CM Diagnosis Code*</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>M72.0</td>
<td>Palmar fascial fibromatosis (Dupuytren)</td>
</tr>
<tr>
<td>N48.6</td>
<td>Induration penis plastica</td>
</tr>
</tbody>
</table>

X. POLICY HISTORY

MP-2.153
CAC 9/29/10- New policy.
CAC 10/25/11 Consensus Review. BCBSA Background/Description adopted.
CAC 2/28/12 Revised policy criteria from investigational to medically necessary for the treatment of Dupuytren’s contracture in adult patients with a palpable cord, for up to three injections at intervals of at least thirty days.
CAC 6/4/13 Consensus review. No change to policy statements. References updated.
Admin change 1/2014 Removed retired Novitas Solutions Local Coverage Determination (LCD) L31171 Injectable Collagenase Clostridium Histolyticum for Dupuytren’s Contracture.
CAC 1/28/14 Minor revision. Policy being revised to add new FDA-approved indication for the treatment of Peyronie’s Disease. Xiaflex is now considered medically necessary 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. This indication was previously considered investigational. References updated. Rationale added. Medicare variation removed as this LCD was retired 11/01/13. Added dx 687.85.
Admin change 5/30/14 Rationale updated regarding Peyronie’s Disease.

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[Note: Final page is signature page and is kept on file, but not issued with Policy.]