MEDICAL POLICY

MEDICAL POLICY DETAILS	
Medical Policy Title	**COLLAGENASE CLOSTRIDIUM HISTOLYTICUM (XIAFLEX) FOR FIBROPROLIFERATIVE DISORDERS**
Policy Number	**5.01.15**
Category	**Technology Assessment**
Effective Date	**06/17/10**
Revised Date	**08/18/11, 01/19/12, 12/20/12, 12/19/13, 01/22/15, 02/18/16, 03/16/17, 02/15/18, 03/21/19, 1/16/20**
Product Disclaimer	• *If a product excludes coverage for a service, it is not covered, and medical policy criteria do not apply.* • *If a commercial product (including an Essential Plan product) or a Medicaid product covers a specific service, medical policy criteria apply to the benefit.* • *If a Medicare product covers a specific service, and there is no national or local Medicare coverage decision for the service, medical policy criteria apply to the benefit.*

POLICY STATEMENT

I. Based upon our criteria and assessment of peer-reviewed literature, up to three injections of collagenase clostridium (e.g., Xiaflex) has been medically proven effective and, therefore, can be considered as a **medically appropriate** treatment option in the management of adults with Dupuytren's contracture in either the metacarpophalangeal (MCP) or proximal interphalangeal (PIP) joint when there is a palpable palmar cord.

II. Based upon our criteria and assessment of peer-reviewed literature, a treatment course of up to four cycles of injectable collagenase clostridium (e.g., Xiaflex) has been medically proven to be effective and, therefore, is considered a **medically appropriate** treatment option for adults with Peyronie's disease, when ALL of the following criteria are met:
   A. Stable disease, as defined by no change in symptoms (e.g., penile curvature and pain) for at least six months;
   B. Presence of a palpable, non-calcified plaque at the site of maximum curvature (as determined by penile ultrasound);
   C. Objective documentation at the start of therapy of a curvature deformity between 30 and 90 degrees that causes a functional deficit (i.e. an inability to engage in sexual intercourse, or sexual intercourse is painful for either partner) not attributable to other causes; and
   D. Injectable collagenase clostridium (e.g., Xiaflex) will be used in combination with a penile modeling procedure.

III. Based upon our criteria and assessment of peer-reviewed literature, continued clostridial collagenase histolyticum injections for the treatment of Peyronie's disease are considered **not medically necessary** when the penis is functionally straight (i.e. the curvature deformity is less than or equal to 20 degrees) after the first, second or third treatment cycle, or if further treatment is not clinically indicated.

IV. Based upon our criteria and lack of peer-reviewed literature, a clostridial collagenase histolyticum injection treatment course beyond four cycles per plaque has not been medically proven to be effective and is, therefore, considered **investigational** for the treatment of Peyronie's disease.

V. Based upon our criteria and assessment of peer-reviewed literature, injectable collagenase clostridium (e.g., Xiaflex) has not been medically proven to be effective and is considered **investigational** for all other indications, including, but not limited to, adhesive capsulitis of the shoulder.

Refer to Corporate Medical Policy #7.01.11 Cosmetic and Reconstructive Procedures.

Refer to Corporate Medical Policy #11.01.03 Experimental or Investigational Services.

POLICY GUIDELINES

I. For Dupuytren's contracture, collagenase clostridium is administered at four-week intervals for a total of three injections (0.58 mg) per cord. Each injection is followed by manual manipulation of the affected joint.

II. For Peyronie's disease, a treatment course consists of a maximum of four treatment cycles, each separated by six weeks. Each treatment cycle consists of two Xiaflex injection procedures and one penile modeling procedure.

III. Cosmetic procedures are performed to reshape structures of the body in order to improve the patient's appearance and self-esteem. Clostridial collagenase histolyticum injection treatment is considered a cosmetic procedure and **not medically necessary** when there is no functional deficit present.

IV. The Federal Employee Health Benefit Program (FEHBP/FEP) requires that procedures, devices or laboratory tests approved by the U.S. Food and Drug Administration (FDA) may not be considered investigational and thus these procedures, devices or laboratory tests may be assessed only on the basis of their medical necessity.

DESCRIPTION

Fibroproliferative disorders, characterized by excessive collagen deposits, can affect the musculoskeletal system, causing pain, limiting joint range of motion, and negatively impacting quality of life. Examples of these fibrotic tissue disorders include Dupuytren's contracture, adhesive capsulitis, and Peyronie's disease.

Collagenases, enzymes that digest native collagen and lead to the disruption of contracted cords, are being investigated as a non-surgical treatment for fibroproliferative disorders. Injection of collagenase clostridium histolyticum, a bacterial collagenase, is intended to provide a non-operative treatment option and is usually an office-based procedure. Its use in the treatment of Dupuytren's contracture has been the most widely studied. Therapy consists of up to three injections into a palpable cord at four-week intervals, followed by manual manipulation of the affected joint to attempt rupture of the cord.

RATIONALE

In February 2010, the FDA approved Auxilium Pharmaceutical Inc.'s biologics license application for clostridium 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 three injections at four-week intervals may be given into a palpable Dupuytren's cord with a contracture of a metacarpophalangeal (MP) joint or a proximal interphalangeal (PIP) joint. The FDA expanded the indications (October 2014) for Xiaflex for Dupuytren's contracture, to allow up to two joints to be injected in the same hand during one treatment visit. The expanded indications were partially based on data from the MULTICORD study (RG Gaston, *et al*. 2015). The MULTICORD study enrolled 715 patients (725 treated joint pairs), and 714 patients (724 joint pairs) were analyzed for efficacy. At day 31, mean total fixed flexion contracture (sum of two treated joints) decreased 74%, from 98° to 27°. Mean total range of motion increased from 90° to 156°. The incidence of clinical success was 65% in metacarpophalangeal joints and 29% in proximal interphalangeal joints. Most treatment-related AEs were mild to moderate, resolving without intervention; the most common were swelling of treated extremity, contusion, and pain in extremity.

While the evidence of long-term recurrence rates is not yet available, the outcomes from clinical trials thus far suggest that injectable collagenase clostridium provides short-term release of contracture in patients with Dupuytren's disease. Longer-term studies and comparative studies to surgical intervention are still needed to determine the overall safety and effectiveness of this therapy. Five-year follow-up data from the Cordless registry were reported by Peimer, *et al*. (2015). Recurrence occurred in 47% of successfully treated joints.

On December 6, 2013, the FDA approved collagenase clostridium histolyticum (CCH, Xiaflex) as treatment for men with Peyronie's disease who have a penile curvature of at least thirty degrees. According to the FDA, CCH will be available only through a Risk Evaluation and Mitigation Strategy (REMS), a stipulation the FDA places on approved therapies when a risk of potentially serious adverse effects exists, in this case, penile fracture and other serious injuries to the penis.

This mirrors the REMS requirement that accompanied the FDA approval for Dupuytren's contracture in 2010. The REMS for CCH requires healthcare professionals to complete a training program for administration of CCH to patients with Peyronie's disease. Per the manufacture's web site, the dose of CCH is 0.58 mg per injection administered into a Peyronie's plaque. Up to eight injections (four treatment cycles) may be administered in the course of treatment. Also, a penile modeling procedure is recommended after every treatment cycle of two injections in an effort to further disrupt the plaque. Expert opinion defines "functionally straight" as penile curvature less than or equal to 20 degrees (Levine and Larsen, 2013 and Krishnappa et al. 2019).

In 2013, Gelbard and colleagues published the results of two double-blind, placebo-controlled RCTs, IMPRESS (Investigation for Maximal Peyronie's Reduction Efficacy and Safety Studies) I and II, which examined the clinical efficacy and safety of collagenase injections in subjects with Peyronie disease. 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 two studies examined collagenase injections in 417 and 415 participants, respectively, through a maximum of four treatment cycles, each separated by six weeks (for up to eight 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 three cases and penile hematoma in the other three cases. The three corporeal ruptures and one hematoma were successfully repaired surgically. Of the two remaining penile hematomas, one case was successfully resolved without intervention and the other resolved with aspiration.

In a prospective cohort study by Wymer and colleagues (2018), 115 patients with PD who completed at least two CCH cycles were analyzed for improvement in penile curvature in order to assess for characteristics predictive of treatment success. Thirty-four (34%) of the 115 men included were found to have calcification. Patients with calcified plaque were more likely to have dorsal curvature and severe erectile dysfunction. Patients with noncalcified plaque and curvature of at least 60 degrees had the greatest improvement in curvature (defined as improvement in curvature greater than 20%). The authors concluded that calcification is one of the strongest predictors for CCH failure and men with baseline curvature greater than 60 degrees are approximately 2.5 times more likely to experience a 20% or more improvement compared to lesser curvatures.

Use of this biologic material for treatment of conditions (e.g., adhesive capsulitis) other than Dupuytren's and Peyronie's disease is an off-label application.

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

CODES

- *Eligibility for reimbursement is based upon the benefits set forth in the member's subscriber contract.*
- *CODES MAY NOT BE COVERED UNDER ALL CIRCUMSTANCES. PLEASE READ THE POLICY AND GUIDELINES STATEMENTS CAREFULLY.*
- *Codes may not be all inclusive as the AMA and CMS code updates may occur more frequently than policy updates.*

CPT Codes

Code	Description
20527	Injection, enzyme (e.g., collagenase), palmar fascial cord (e.g., Dupuytren's contracture)
26341	Manipulation, palmar fascial cord (e.g., Dupuytren's contracture), post enzyme injection (e.g., collagenase), single cord
While there are no specific CPT codes for the injection of collagenase for Peyronie's disease, the American Urological Association has recommended the following CPT codes for the use of Xiaflex for Peyronie's disease.	
54235	Injection of corpora cavernosa with pharmacologic agent(s) (e.g., papaverine, phentolamine)
54200	Injection procedure for Peyronie's disease
54205	Injection procedure for Peyronie disease; with surgical exposure of plaque
96372	Therapeutic, prophylactic, or diagnostic injection (specify substance or drug); subcutaneous or intramuscular

HCPCS Codes

Code	Description
J0775	Injection, collagenase clostridium histolyticum, 0.01mg

ICD10 Codes

Code	Description
M72.0	Palmer fascial fibromatosis (Dupuytren)
M75.00-M75.02 **(E/I)**	Adhesive capsulitis of shoulder (code range)
N48.6	Induration penis plastica (Peyronie's disease)

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*Key Article

KEY WORDS

Collagenase clostridium injection, collagenase injection, Dupuytren's contracture, Peyronie's disease, Xiaflex

CMS COVERAGE FOR MEDICARE PRODUCT MEMBERS

There is currently a Local Coverage Determination (LCD) for Drugs and Biologicals. Please refer to the following LCD website for Medicare Members: https://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=33394&ver=35&SearchType=Advanced&CoverageSelection=Both&NCSelection=NCA%7cCAL%7cNCD%7cMEDCAC%7cTA%7cMCD&ArticleType=SAD%7cEd&PolicyType=Both&s=41&KeyWord=drugs&KeyWordLookUp=Title&KeyWordSearchType=Exact&kq=true&bc=IAAAACAAAAAA&