

## Corporate Medical Policy

### Injectable Clostridial Collagenase for Fibroproliferative Disorders

**File Name:** injectable\_clostridial\_collagenase\_for\_fibroproliferative\_disorders  
**Origination:** 6/2010  
**Last CAP Review:** 11/2020  
**Next CAP Review:** 2/2021  
**Last Review:** 11/2020

#### Description of Procedure or Service

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

Injection with clostridial collagenase is intended to provide a non-operative 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. Examples of fibroproliferative disorders include Dupuytren's disease, adhesive capsulitis, and Peyronie's disease.

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 non-steroidal anti-inflammatory drugs. Corticosteroid injection is used with caution. The prevalence of Dupuytren's disease and adhesive capsulitis is estimated at 3% to 6% and 2% to 3%, respectively, in the general population and increases with advancing age. Both conditions are more common in patients with diabetes or thyroid disease. Dupuytren'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% to 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. 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), penile implant, or a combination of these.

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.

## Regulatory Status

In February 2010, the FDA (United States Food and Drug Administration) approved Auxilium Pharmaceutical Inc.'s biologics license application (BLA) 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. In October 2014, FDA approved labeling for Xiaflex® stating that up to two cords in the same hand may be injected at a single treatment visit.

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

**\*\*\*Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.**

## **Policy**

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**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 for the treatment of Peyronie's disease in adult patients with a palpable penile plaque and a penile curvature deformity of at least 30 degrees at the start of therapy may be considered medically necessary, for a maximum of four treatment cycles.**

**Injectable clostridial collagenase is considered investigational for all other indications including, but not limited to, adhesive capsulitis. BCBSNC does not provide coverage for investigational services or procedures.**

## **Benefits Application**

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This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

Some benefit plans exclude treatment of Peyronie's disease as a benefit exclusion. Please refer to member booklet for availability of benefits.

## **When Injectable Clostridial Collagenase is covered**

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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. Up to 2 cords in the same hand may be injected at a single treatment visit.

Injectable clostridial collagenase for the treatment of Peyronie's disease in adult patients with a palpable penile plaque and a penile curvature deformity of at least 30 degrees at the start of therapy may be considered medically necessary, for a maximum of four treatment cycles.

## **When Injectable Clostridial Collagenase is not covered**

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Injectable clostridial collagenase is considered investigational for all other clinical indications, including, but not limited to adhesive capsulitis.

## **Policy Guidelines**

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For individuals who have Dupuytren's 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 include symptoms, change in disease status, functional outcomes, and quality of life. 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, randomized studies with direct comparisons are not available. Some nonrandomized studies comparing clostridial collagenase with surgery report similar outcomes with faster return-to-work and return-to-usual activities rates with clostridial collagenase, but one study reported poorer contraction improvement but lower adverse event rates. Evidence on long-term recurrence rates is somewhat limited, but 3- and 5-year follow-up from one large registry reported high recurrence rates (47% at 5 years). 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 individuals who have Peyronie's 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's disease. However, evidence demonstrating improvements in health outcome is lacking, as are studies comparing clostridial collagenase with other therapies for Peyronie's disease. Despite the important uncertainties that remain in the peer-reviewed scientific literature limiting determination of the effect of the technology on net health outcomes; the 2010 U.S. Food and Drug Administration labeling and the 2015 American Urological Association guidelines identify a patient population for use of intralesional collagenase *Clostridium histolyticum* in combination with modeling in patients with stable Peyronie's disease, penile curvature greater than 30° and less than 90°, and intact erectile function.

Because of the risks of corporal rupture or other serious penile injury, XIAFLEX is available for the treatment of Peyronie's disease only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the XIAFLEX REMS Program.

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

## **Billing/Coding/Physician Documentation Information**

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This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at [www.bcbsnc.com](http://www.bcbsnc.com). They are listed in the Category Search on the Medical Policy search page.

*Applicable codes: 20527, 20550, 26341, 26989, 54200, 54205, 54235, J0775*

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

## Scientific Background and Reference Sources

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BCBSA Medical Policy Reference Manual [Electronic Version]. 5.01.19, 3/11/10.

Food and Drug Administration (FDA). BLA Approval for Xiaflex, clostridial collagenase histolyticum, Auxilium Pharmaceuticals, Inc. Retrieved on May 6, 2010 from [http://www.accessdata.fda.gov/drugsatfda\\_docs/applletter/2010/125338s000ltr.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/applletter/2010/125338s000ltr.pdf)

Hurst LC, Badalamente MA, Wang ED. (2009). Injectable Clostridial Collagenase: Striving Toward Non-Operative Treatment Options For Fibroproliferative Disorders. Retrieved on May 6, 2010 from [http://www.aaos.org/research/committee/research/Kappa/KD2009\\_Hurst.pdf](http://www.aaos.org/research/committee/research/Kappa/KD2009_Hurst.pdf)

Senior Medical Director review 5/17/2010

Specialty Matched Consultant Advisory Panel review 7/2010

Food and Drug Administration (FDA). Warning Letter and Notice of Violation. June 10, 2010. Retrieved on January 21, 2011 from <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/WarningLettersandNoticeofViolationLetterstoPharmaceuticalCompanies/UCM215799.pdf>

Specialty Matched Consultant Advisory Panel review 2/2011

BCBSA Medical Policy Reference Manual [Electronic Version]. 5.01.19, 3/10/11

BCBSA Medical Policy Reference Manual [Electronic Version]. 5.01.19, 11/10/11

Medical Director review 12/2011

Specialty Matched Consultant Advisory Panel review 2/2012

BCBSA Medical Policy Reference Manual [Electronic Version]. 5.01.19, 9/13/12

Bainbridge C, Gerber RA, Szczypa PP, Smith T, Kushner H, Cohen B, Hellio Le Graverand-Gastineau MP. Efficacy of collagenase in patients who did and did not have previous hand surgery for Dupuytren's contracture. *J Plast Surg Hand Surg.* 2012 Sep;46(3-4):177-83. Retrieved from <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3469218/>

Coleman S, Gilpin D, Tursi J, Kaufman G, Jones N, Cohen B. Multiple concurrent collagenase clostridium histolyticum injections to Dupuytren's cords: an exploratory study. *BMC Musculoskelet Disord.* 2012 Apr 27;13:61. Retrieved from <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3409044/>

Specialty Matched Consultant Advisory Panel review 2/2013

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* 2013; 38(1):2-11.

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* 2013; 38(1):12-22.

BCBSA Medical Policy Reference Manual [Electronic Version]. 5.01.19, 10/10/13

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 2013; 190(1):199-207.

Food and Drug Administration (FDA). FDA Press Release. FDA approves first drug treatment for Peyronie's disease. December 6, 2013.  
<http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm377849.htm>

Specialty Matched Consultant Advisory Panel review 2/2014

Medical Director review 3/2014

US Food and Drug Administration (FDA). Highlights of prescribing information: Xiaflex. 2013;  
[http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2013/125338s00611bl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/125338s00611bl.pdf). Last accessed November, 2014.

BCBSA Medical Policy Reference Manual [Electronic Version]. 5.01.19, 10/09/2014

Specialty Matched Consultant Advisory Panel (Urology) 11/2014

Medical Director review 11/2014

Specialty Matched Consultant Advisory Panel (Orthopedics) 2/2015

Medical Director review 2/2015

BCBSA Medical Policy Reference Manual [Electronic Version]. 5.01.19, 10/15/2015

Specialty Matched Consultant Advisory Panel (Urology) 11/2015

Specialty Matched Consultant Advisory Panel (Orthopedics) 2/2016

BCBSA Medical Policy Reference Manual [Electronic Version]. 5.01.19, 10/13/2016

Specialty Matched Consultant Advisory Panel (Urology) 11/2016

Specialty Matched Consultant Advisory Panel (Orthopedics) 2/2017

Specialty Matched Consultant Advisory Panel (Urology) 11/2017

BCBSA Medical Policy Reference Manual [Electronic Version]. 5.01.19, 12/14/2017

Specialty Matched Consultant Advisory Panel (Orthopedics) 2/2018

BCBSA Medical Policy Reference Manual [Electronic Version]. 5.01.19, 10/10/2018

Specialty Matched Consultant Advisory Panel (Urology) 11/2018

Specialty Matched Consultant Advisory Panel (Orthopedics) 2/2019

BCBSA Medical Policy Reference Manual [Electronic Version]. 5.01.19, 10/17/2019

Specialty Matched Consultant Advisory Panel (Urology) 11/2019

Specialty Matched Consultant Advisory Panel (Orthopedics) 2/2020

## **Policy Implementation/Update Information**

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- 06/08/10 Implementation of new policy titled “Injectable Clostridial Collagenase for Fibroproliferative Disorders”. Injectable clostridial collagenase is considered investigational for all indications including, but not limited to, Dupuytren’s contracture, Peyronie’s disease, and adhesive capsulitis. Added CPT code C9266. (mco)
- 8/17/10 Specialty Matched Consultant Advisory Panel review 7/2010. No change in policy statement. (mco)
- 10/12/10 Added codes J3490 and J9999 to Billing/Coding section (mco)
- 1/4/11 Codes J3490, J3590, J9999 and C9266 deleted from policy. New code specific to injection of Clostridial Collagenase (Xiaflex) added to Billing/Coding section: **J0775**. (mco)
- 3/15/11 Specialty Matched Consultant Advisory Panel review 2/2011. References updated. (mco)
- 5/24/11 References updated. No changes to policy statements. (mco)
- 12/30/11 Policy Statements revised as follows: “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 is considered investigational for all other indications including, but not limited to, Peyronie’s disease, and adhesive capsulitis.” “When Covered” and “When not Covered” sections revised to reflect coverage criteria. CPT codes 20527 and 26341 added to

- “Billing/Coding” section and are effective 1/1/2012. CPT code 26989 deleted. “Policy Guidelines” section updated. References updated. (mco)
- 3/20/12 Specialty Matched Consultant Advisory Panel review 2/2012. No changes to Policy Statements. (mco)
- 11/27/12 References updated. No changes to policy statements. (mco)
- 3/12/13 References updated. Policy Guidelines updated. Specialty Matched Consultant Advisory Panel review 2/2013. No changes to Policy Statements. (mco)
- 11/26/13 Description section updated. References updated. No changes to Policy Statements. (mco)
- 3/11/14 References updated. Description section updated. Specialty Matched Consultant Advisory Panel review 2/2014. Medical Director review 2/2014. No changes to Policy Statements. (mco)
- 3/31/15 Added the following statement to the Billing/Coding section: “Some benefit plans exclude treatment of Peyronie’s disease as a benefit exclusion. Please refer to member booklet for availability of benefits.” Description section, Regulatory Status, and Policy Guidelines section updated with information related to the use of Xiaflex in the treatment of Peyronie’s disease. References added. Specialty Matched Consultant Advisory Panel review 11/24/2014. Added 54200, 54205, and 54235 to Billing/Coding section. Treatment of Peyronie’s disease added to When Covered section. Added “Up to 2 cords in the same hand may be injected at a single treatment visit” to the When Covered section. Specialty Matched Consultant Advisory Panel review 2/25/2015. (sk)
- 12/30/15 Reference added. Specialty Matched Consultant Advisory Panel (Urology) review 11/18/2015. (sk)
- 4/1/16 Specialty Matched Consultant Advisory Panel (Orthopedics) review 2/24/2016. (sk)
- 1/27/17 Reference added. Specialty Matched Consultant Advisory Panel (Urology) review 11/30/2016. (sk)
- 3/31/17 Specialty Matched Consultant Advisory Panel (Orthopedics) review 2/22/2017. (sk)
- 12/15/17 Specialty Matched Consultant Advisory Panel (Urology) review 11/29/2017. (sk)
- 1/26/18 Reference added. (sk)
- 4/27/18 Specialty Matched Consultant Advisory Panel (Orthopedics) review 2/28/2018. (sk)
- 12/14/18 References added. Specialty Matched Consultant Advisory Panel (Urology) review 11/28/2018. No change to policy intent. (krc)
- 3/12/19 Specialty Matched Consultant Advisory Panel (Orthopedics) review 2/20/2019. (krc)
- 12/2/19 References added. Specialty Matched Consultant Advisory Panel (Urology) review 11/20/2019. No change to policy intent. (krc)
- 3/10/20 Specialty Matched Consultant Advisory Panel (Orthopedics) review 2/19/2020. No change to policy statements. (krc)
- 12/31/20 Updated Policy Guidelines with additional clinical evidence summary for Peyronie’s disease. Reference added. Specialty Matched Consultant Advisory Panel (Urology) review 11/18/2020. No change to policy statements. (krc)

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Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.