Introduction

Dupuytren’s contracture is a hand condition where knots of tissue form beneath the skin of the palm. Over time these knots create a cord, which pulls on one or more fingers. The cord is inflexible, causing the fingers to curl into a bent position. The ring finger and pinky fingers are usually affected, with the middle finger affected less often. It’s rare that the index finger and thumb are affected. The condition advances slows and usually starts with a thickening of skin on the palm. A knot then forms, followed by another and another. Men older than 50 and of northern European descent have the highest incidence of Dupuytren contracture. There are a few treatment options, one of which calls for injecting a specific enzyme (clostridial collagenase) into the cord. The enzyme makes the cord softer, allowing it to stretch and break as a doctor straightens the fingers. The enzyme also has been used to try to treat other conditions. This policy describes the conditions for which injections of this enzyme may be considered medically necessary.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.
## Policy Coverage Criteria

<table>
<thead>
<tr>
<th>Indication</th>
<th>Medical Necessity</th>
</tr>
</thead>
</table>
| **Dupuytren contracture** | Injectable clostridial collagenase (Xiaflex®) may be considered medically necessary for the treatment of Dupuytren contracture in adult patients with a palpable cord, for up to 3 injections at intervals of at least 30 days.  
  - Physicians should treat no more than 2 joints in the same hand for Dupuytren contracture per treatment visit, consistent with U.S. Food and Drug Administration (FDA) labeling. |
| **Peyronie’s disease**     | Injectable clostridial collagenase (Xiaflex®) may be considered medically necessary for the treatment of Peyronie’s disease.  
  - **Note:** The treatment of sexual dysfunction is excluded under many benefit plans, regardless of the underlying condition. Therefore, use of Xiaflex for Peyronie’s disease may not be covered. Please refer to the applicable benefit plan document to determine benefit availability (see Benefit Application for further information). |

<table>
<thead>
<tr>
<th>Indication</th>
<th>Investigational</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adhesive capsulitis</strong></td>
<td>Injectable clostridial collagenase (Xiaflex®) is considered investigational for all other indications including, but not limited to, adhesive capsulitis.</td>
</tr>
<tr>
<td><strong>Other indications</strong></td>
<td></td>
</tr>
</tbody>
</table>

### Documentation Requirements

The patient’s medical records submitted for review should document that medical necessity criteria are met. The record should include clinical documentation of:

- Diagnosis/condition
- History and physical examination documenting the severity of the condition

### Coding
<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT</td>
<td></td>
</tr>
<tr>
<td>20527</td>
<td>Injection, enzyme (eg, collagenase), palmar fascial cord (ie, Dupuytren’s contracture)</td>
</tr>
<tr>
<td>26341</td>
<td>Manipulation, palmar fascial cord (ie, Dupuytren’s cord), post enzyme injection (eg, collagenase), single cord</td>
</tr>
<tr>
<td>54200</td>
<td>Injection procedure for Peyronie disease</td>
</tr>
<tr>
<td>54205</td>
<td>Injection procedure for Peyronie disease; with surgical exposure of plaque</td>
</tr>
<tr>
<td>54235</td>
<td>Injection of corpora cavernosa with pharmacologic agent(s) (eg, papaverine, phentolamine)</td>
</tr>
<tr>
<td>HCPCS</td>
<td></td>
</tr>
<tr>
<td>J0775</td>
<td>Injection, collagenase clostridium histolyticum, 0.01 mg</td>
</tr>
</tbody>
</table>

**Note:** CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). HCPCS codes, descriptions and materials are copyrighted by Centers for Medicare Services (CMS).

### Related Information

**Benefit Application**

Some plans may require prior authorization before injection of collagenase clostridium histolyticum. For questions about benefit information, providers should contact customer service using the telephone number on the back of the member’s identification card.

Many benefit plans exclude the diagnosis and treatment of sexual dysfunctions, regardless of origin or cause; surgical, medical, or psychological, including drugs, medications, or implants; and any direct or indirect complications and aftereffects thereof. Please refer to the applicable benefit plan to determine benefit availability and the terms, conditions, and limitations of coverage.

### Evidence Review
Description

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

Background

Fibroproliferative Disorders

Fibrotic tissue disorders, characterized by excessive collagen deposits, can affect the musculoskeletal system, causing pain and limiting movement and reducing joint range of motion. Examples of fibroproliferative disorders include Dupuytren disease, Peyronie disease, and adhesive capsulitis. The mechanisms that contribute to the pathology are poorly understood.

Dupuytren Disease

In Dupuytren disease, collagen deposition in nodules and cords in the palm and fingers results in pitting of the overlying cutis and flexion contractures. The prevalence of Dupuytren disease is estimated at 3% to 6% in the general population and increases with advancing age. The disease is more common in people with diabetes or thyroid disease and among men.¹

Treatment

The standard of care for Dupuytren disease is surgery, most commonly open fasciectomy. Other surgical procedures are percutaneous fasciotomy and needle fasciotomy. Surgery is recommended in patients with functional impairment and metacarpophalangeal joint contractures of 30° or more. There is no effective pharmacotherapy.

Peyronie Disease

Peyronie disease is the development of abnormal scar tissue, or plaques, in the tunica albuginea layer of the penis causing distortion, curvature, and pain (usually during erection). It occurs in 3% to 9% of men, most commonly between the ages of 45 and 60 years. In some cases, plaque
does not cause severe pain or curvature, and the condition resolves on its own. In severe cases, erectile dysfunction can occur.

**Treatment**

The goal of treatment is to reduce pain and maintain sexual function. Treatments in early stages (before calcification) include vitamin E or para-aminobenzoate tablets (eg, Potaba), although studies of oral therapies have demonstrated inconsistent benefit. Intralesional injection therapy consisting of injection of interferon-α-2b or calcium channel-blockers (eg, verapamil) is the current standard of therapy.\(^2\) Surgical procedures involve the excision of hardened tissue and skin graft, the removal or pinching (plication) of tissue opposite the plaque to reduce curvature (the Nesbit procedure), penile implant, or a combination of these.

**Adhesive Capsulitis**

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

**Treatment**

Adhesive capsulitis or “frozen shoulder” is treated with physical therapy and mobilization in combination with analgesics or nonsteroidal anti-inflammatory drugs. Corticosteroid injection is used with caution.

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

**Summary of Evidence**

For individuals who have Dupuytren contracture who receive local clostridial collagenase injection(s), the evidence includes several placebo-controlled, randomized trials, nonrandomized
comparative studies, and single-arm studies, along with systematic reviews of these studies. Relevant outcomes are symptoms, change in disease status, functional outcomes, and quality of life. The evidence from clinical trials has suggested that injectable clostridial collagenase provides short-term release of contracture. A comparison of overall outcomes compared with surgical intervention may be useful; however, randomized studies with direct comparisons are not available. Some nonrandomized studies comparing clostridial collagenase with surgery reported similar outcomes with faster return-to-work and return-to-usual activities rates with clostridial collagenase, but 1 study reported poorer contraction improvement though lower adverse event rates. Evidence on long-term recurrence rates is somewhat limited, but 3-year and 5-year follow-ups from a large registry reported high recurrence rates (47% at 5 years). Although clostridial collagenase offers the potential benefit of less-invasive treatment for Dupuytren contracture, gaps in the evidence base related to treatment durability exist. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have Peyronie disease who receive local clostridial collagenase injection(s), the evidence includes two 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 self-reported distress from symptoms related to Peyronie disease. However, evidence demonstrating improvements in health outcome is lacking, as are studies comparing clostridial collagenase with other therapies for Peyronie disease. The evidence is insufficient to determine the effects of the technology on health outcomes. However, based on the American Urological Association recommendation, the Plan will allow clostridial collagenase (Xiaflex®) injections as medically necessary if the member has a benefit for treatment of a sexual dysfunction.

For individuals who have adhesive capsulitis who receive local clostridial collagenase injection(s), the evidence is very limited. Relevant outcomes are symptoms, change in disease status, functional outcomes, and quality of life. No published literature 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.

**Ongoing and Unpublished Clinical Trials**

Some currently unpublished trials that might influence this policy are listed in Table 1.
## Table 1. Summary of Key Trials

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

ISRCTN: International Standard Randomised Controlled Trials Number  
NCT: national clinical trial  
* Denotes industry-sponsored or cosponsored trial
Clinical Input from Physician Specialty Societies and Academic Medical Centers

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

2011 Input

In response to requests, 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 contracture, noting lack of long-term data and head-to-head trials comparing collagenase with surgical options. However, despite considering this treatment investigational due to insufficient long-term evidence of effectiveness, another reviewer noted that injectable clostridial collagenase for Dupuytren contracture is approved by the U.S. Food and Drug Administration, and there is evidence of short-to-medium-term effectiveness available. Five reviewers indicated injectable clostridial collagenase for Dupuytren contracture may be considered medically necessary; they noted this is a treatment alternative to surgery. This recommendation was considered to be near-uniform support for the medical necessity of injectable clostridial collagenase for the treatment of Dupuytren contracture.

Four reviewers agreed that injectable clostridium collagenase is investigational for the treatment of Peyronie disease. One of these reviewers also commented that, while this treatment is considered investigational, it may be indicated for Peyronie disease when it is bothersome, noting that surgery is intrusive. Four reviewers also agreed injectable clostridium collagenase is investigational for the treatment of adhesive capsulitis. Finally, 6 reviewers agreed injectable clostridium collagenase is investigational for all other indications.

2010 Input

In response to requests, input was received from 6 academic medical centers while this policy was under review in 2010. The input was mixed, with half of those providing comments agreeing that use of this agent is investigational. While there was support for use in Dupuytren
contracture, comments were made about the limited amount of data on long-term outcomes and durability.

**Practice Guidelines and Position Statements**

**Dupuytren Contracture**

**National Institute for Health and Care Excellence**

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

**American Urological Association**

The American Urological Association (2018) issued guidelines for the diagnosis and treatment of Peyronie disease. For patients with stable Peyronie disease, penile curvature greater than 30° and less than 90°, and intact erectile function (with or without the use of medications), the Association recommended intralesional collagenase Clostridium histolyticum in combination with modeling (moderate recommendation; evidence strength grade B).

**European Association of Urology**

The European Association of Urology (2012) guidelines on penile curvature indicate injectable collagenase is a treatment option for Peyronie disease based on evidence rated as level 2b (“Evidence obtained from at least one other type of well-designed quasi-experimental study”) and grade C (“Made despite the absence of directly applicable clinical studies of good quality”).
**Adhesive Capsulitis**

**National Institute for Health Research**

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

**Medicare National Coverage**

There is no national coverage determination.

**Regulatory Status**

Table 2 lists indications for clostridial collagenase (Xiaflex®; Auxilium Pharmaceuticals [Norristown, PA]) that have been approved by the Food and Drug Administration.

### Table 2. FDA-Approved Indications for Clostridial Collagenase (Xiaflex®)

<table>
<thead>
<tr>
<th>Indication</th>
<th>Approved</th>
<th>Indications</th>
<th>Additional Information</th>
</tr>
</thead>
</table>
| Dupuytren contracture | 2010     | - Adults with Dupuytren contracture with a palpable cord  
- Up to 3 injections at 4-week intervals into a palpable Dupuytren cord with a contracture of a metacarpophalangeal or a proximal interphalangeal joint | • Approval accompanied by REMS. The manufacturer must:  
  o Evaluate and mitigate risks and serious adverse events  
  o Instruct health care providers on procedure to inject Xiaflex and perform finger extension procedures  
  o Inform patients of potential risks of treatment                                                                |
|                       | 2014     | Indication expanded: up to 2 joints in same hand may be treated during a treatment visit                                                                                                                   |                                                                                           |
| Peyronie disease      | 2013     | - Men with a palpable penile plaque and penile curvature more than 30 degrees  
- A maximum of 4 cycles, each of which consists of 2 Xiaflex® injection procedures | • Approval accompanied by black box warning of corporal rupture and penile hematoma  
• Only available through a restricted program, Xiaflex REMS, due to risk of corporal rupture. REMS requirements:  
  o Prescribers must enroll and complete training in the administration of Xiaflex for the treatment of Peyronie disease                                                                                   |
Indication | Approved | Indications | Additional Information
--- | --- | --- | ---
| | | | o Health care sites must be certified with the program and ensure that only certified prescribers administer Xiaflex

Adapted from Food and Drug Administration (2018)³

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

References


History

<table>
<thead>
<tr>
<th>Date</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>04/01/19</td>
<td>New policy, approved March 19, 2019. This policy replaces policy 5.01.19 which is now deleted. Injectable clostridial collagenase may be considered medically necessary when criteria are met, considered non-covered for treatment of Peyronie's disease, considered investigational for all other indications.</td>
</tr>
<tr>
<td>09/01/19</td>
<td>Interim Review, approved August 13, 2019. Policy statement changed: Injectable clostridial collagenase may be considered medically necessary for the treatment of Peyronie's disease (in accordance to the member contract, if the member has a treatment of sexual dysfunction benefit; otherwise it is considered a contractual exclusion if the member has no benefit for treatment of a sexual dysfunction).</td>
</tr>
</tbody>
</table>
Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and local standards of practice. Since medical technology is constantly changing, the Company reserves the right to review and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit booklet or contact a member service representative to determine coverage for a specific medical service or supply. CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). ©2019 Premera All Rights Reserved.

Scope: Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.
Discrimination is Against the Law

Premera Blue Cross complies with applicable Federal civil rights laws and does not discriminate on the basis of race, color, national origin, age, disability, or sex. Premera does not exclude people or treat them differently because of race, color, national origin, age, disability or sex.

Complaints and appeals can be filed in English and in certain other languages. The following is a list of the languages in which complaints and appeals can be filed:

- Arabic
- Amharic
- Chinese
- Creole
- Dutch
- French
- German
- Italian
- Arabic
- Amharic
- Chinese
- Creole
- Dutch
- French
- German
- Italian

You can file a complaint if you believe Premera has failed to provide these services or has discriminated in another way on the basis of race, color, national origin, age, disability, or sex.

If you believe Premera has failed to provide these services or has discriminated in another way on the basis of race, color, national origin, age, disability, or sex, contact the Civil Rights Coordinator.

If you need these services, contact the Civil Rights Coordinator.

Getting Help in Other Languages

This Notice has Important Information. This notice may have important information about your application or coverage through Premera Blue Cross. There may be key dates in this notice. You may need to take action by certain deadlines to keep your healthcare coverage or help with costs. You have the right to get this information and help in your language at no cost. Call 800-722-1471 (TTY: 800-842-5357).

Oromoo (Cushite):

Français (French):

Deutsche (German):

Getting Help in Other Languages

This Notice has Important Information. This notice may have important information about your application or coverage through Premera Blue Cross. There may be key dates in this notice. You may need to take action by certain deadlines to keep your healthcare coverage or help with costs. You have the right to get this information and help in your language at no cost. Call 800-722-1471 (TTY: 800-842-5357).

中文 (Chinese):
本通知有重要的讯息。本通知可能有關於您透過 Premera Blue Cross 提交的申請或保險的重要訊息。本通知內可能有重要日期。您可能需要在截止日期之前採取行動，以保留您的健康保險或費用補貼。您有權利免費以您的母語得到本訊息和幫助。請撥電話 800-722-1471 (TTY: 800-842-5357).

Italiano (Italian):