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 slowly 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’s 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

### Indication | Medical Necessity
--- | ---
**Dupuytren contracture** | Injectable clostridial collagenase 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.

**Note:** Product name: Xiaflex® (collagenase clostridium histolyticum)

### Indication | Investigational
--- | ---
**Peyronie disease**
**Adhesive capsulitis**
**Other indications** | Injectable clostridial collagenase is considered investigational for all other indications including, but not limited to, Peyronie disease and adhesive capsulitis.

**Note:** Product name: Xiaflex® (collagenase clostridium histolyticum)

### Coding

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
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<tr>
<td><strong>CPT</strong></td>
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<tr>
<td>20527</td>
<td>Injection, enzyme (eg, collagenase), palmar fascial cord (ie, Dupuytren’s contracture)</td>
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<tr>
<td>26341</td>
<td>Manipulation, palmar fascial cord (ie, Dupuytren’s cord), post enzyme injection (eg, collagenase), single cord</td>
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<tr>
<td>54200</td>
<td>Injection procedure for Peyronie disease</td>
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<td><strong>HCPCS</strong></td>
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<tr>
<td>J0775</td>
<td>Injection, collagenase clostridium histolyticum, 0.01 mg</td>
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</tbody>
</table>

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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.

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 deposits in nodules and cords in the palm and fingers and results in pitting of the overlying cutis and flexion contractures. The mechanisms that contribute to the pathology are poorly understood. 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 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. 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. Intrallesional 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**

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. 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**

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- and 5-year follow-ups from 1 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 health outcome improvements is lacking. In addition, studies comparing clostridial collagenase with other therapies for Peyronie disease are lacking. The evidence is insufficient to determine the effects of the technology on health outcomes.

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>
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<tbody>
<tr>
<td>Ongoing</td>
<td></td>
<td></td>
<td></td>
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<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 2018</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>Unpublished</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT02193828a</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>
<tr>
<td>NCT02006719a</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>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>NCT02267460a</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 EreCai® Esteem® Manual Vacuum Therapy System in Men With Peyronie’s Disease</td>
<td>30</td>
<td>Mar 2016 (completed)</td>
</tr>
</tbody>
</table>
Clinical Input Received from Physician Specialty Societies and Academic Medical Centers

While the various physician specialty societies and academic medical centers may provide appropriate reviewers who collaborate with and make recommendations during this process, 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, one 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. 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 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 input 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**

In 2017, the National Institute for Health and Care Excellence 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 fasciectomy 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**

In 2015, the American Urological Association (AUA) issued a guideline 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), AUA recommends intralesional collagenase clostridium histolyticum in combination with modeling (Moderate recommendation; Evidence Strength Grade B).

**European Association of Urology**

The 2012 European Association of Urology 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**

In 2012, the National Institute for Health Research published a health technology assessment (HTA) 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 (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

**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-Approval History For Clostridial Collagenase (Xiaflex®)

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

Adapted from Food and Drug Administration (2017).

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

References


References


History

<table>
<thead>
<tr>
<th>Date</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>11/11/13</td>
<td>New Policy. Policy replaces 5.01.524. Considered medically necessary to treat Dupuytren's contracture in adult patients when criteria are met.</td>
</tr>
<tr>
<td>12/17/14</td>
<td>Annual Review. Policy updated with literature review through September 5, 2014. References 3, 5, 10, 13-14, 17-22, 27 added; others renumbered/removed. Rationale section reorganized. Policy statements unchanged. ICD-9 and ICD-10 diagnosis and procedure codes removed; these do not relate to policy adjudication.</td>
</tr>
<tr>
<td>Date</td>
<td>Comments</td>
</tr>
<tr>
<td>------------</td>
<td>----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
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U.S. Department of Health and Human Services
200 Independence Avenue SW, Room 509F, HHH Building Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)

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