Clinical Policy Title: Xiaflex® (collagenase clostridium histolyticum) for Dupuytren’s contractures

Clinical Policy Number: 14.02.01

Effective Date: December 1, 2013
Initial Review Date: July 17, 2013
Most Recent Review Date: August 17, 2016
Next Review Date: August 2017

Related Policies:
None.

ABOUT THIS POLICY: AmeriHealth Caritas Northeast has developed clinical policies to assist with making coverage determinations. AmeriHealth Caritas Northeast’s clinical policies are based on guidelines from established industry sources, such as the Centers for Medicare & Medicaid Services (CMS), state regulatory agencies, the American Medical Association (AMA), medical specialty professional societies, and peer-reviewed professional literature. These clinical policies along with other sources, such as plan benefits and state and federal laws and regulatory requirements, including any state- or plan-specific definition of “medically necessary,” and the specific facts of the particular situation are considered by AmeriHealth Caritas Northeast when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state or federal laws and/or regulatory requirements, the plan benefits and/or state and federal laws and/or regulatory requirements shall control. AmeriHealth Caritas Northeast’s clinical policies are for informational purposes only and not intended as medical advice or to direct treatment. Physicians and other health care providers are solely responsible for the treatment decisions for their patients. AmeriHealth Caritas Northeast’s clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, AmeriHealth Caritas Northeast will update its clinical policies as necessary. AmeriHealth Caritas Northeast’s clinical policies are not guarantees of payment.

Coverage Policy

AmeriHealth Caritas Northeast considers the use of Xiaflex® (collagenase clostridium histolyticum) to be clinically proven; and therefore medically necessary when the following criteria are met:

- Presence of Dupuytren’s contracture of at least 20 degrees and a palpable cord.
- A documented functional impairment as a result of the contracture.
- As an alternative to surgery.
- Procedure is performed in the physician office by an appropriately trained physician (including hand surgeon, orthopedic surgeon, plastic surgeon or general surgeon).
- Adult men, 18 Years and older, with Peyronie’s disease with a palpable plaque and curvature deformity of at least 30 degrees at the start of therapy.

Limitations:
AmeriHealth Caritas Northeast considers the use of Needle Aponeurotomy and splinting to be investigational; and therefore, a finding of medical necessity is not supported.

Because of the risks of corporal rupture (penile fracture) or other serious penile injury in the treatment of Peyronie’s disease, Xiaflex® is available only through the Xiaflex® REMS Program.

<table>
<thead>
<tr>
<th>Required components of the Xiaflex® REMS Program include the following:</th>
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<tr>
<td>• Prescribers must be certified with the program by enrolling and completing training in the administration of Xiaflex® treatment for Peyronie’s disease.</td>
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<tr>
<td>• Healthcare sites must be certified with the program and ensure that Xiaflex® is only dispensed for use by certified prescribers.</td>
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</table>

Further information is available at [www.XiaflexREMS.com](http://www.XiaflexREMS.com)

**Alternative covered services:**

Surgical treatment with release of or disruption of the fibrous band.

**Background**

Dupuytren’s contracture is a progressive thickening of the fibrous bands of the fascial fibers that are located longitudinally in the subcutaneous tissues of the palm. These bands cover the tendons associated with flexion of the fingers. According to the American Academy of Orthopedic Surgeons (AAOS), the etiology of the bands is not known. But contracture occurs because of the thickening and tightening of these bands causing contracture or curling of the affected fingers into flexion. There are a number of associations with Dupuytren’s contracture such as male predominance, Northern European or Scandinavian ancestry, and age. It may be found more commonly in people with diabetes, seizures, or alcoholism. Dolmans and the German and Dutch Dupuytren Study groups have reported finding nine different loci involved in genetic susceptibility. However there is no known association with injury or heavy use of the hand. Pain may be present but is not a hallmark, and when present may resolve over time spontaneously.

On examination the individual may have nodules form in the hand over the palms. These nodules over time will thicken forming dense bands of fibrous tissue with the resulting curling of specific fingers. The severity of the Dupuytren’s contracture is graded according to the Tubiana Grade with the contracture stratified into four stages based upon the Total Passive Extension Deficit (TPED):

- Grade I 0 to 45 degrees TPED
- Grade II 46 to 90 degrees TPED
- Grade III 91 to 135 degrees TPED
- Grade IV is >/= 135 degrees TPED

**Treatment Options:**
Treatments have included surgical management with disruption or removal of the fibrous bands or minimally invasive Needle Aponeurotomy. The latter uses a needle to disrupt the bands. Long-term results are not known so the duration of the positive affect is unknown. For that reason, needle Aponeurotomy is not considered a medically necessary service.

Other treatments have included splinting and steroid injections. Splinting is not generally recognized as helpful as studies have suggested a greater degree of scarring may result from the stretching involved in splinting. For that reason it is not a covered service. The use of steroid injections provides short term benefit with reduction of pain and swelling.

**Xiaflex®/ collagenase clostridium histolyticum:**

In September, 2009, Xiaflex® received FDA approval as a first in class, orphan drug. It is a bacterial collagenase that is injected into the Dupuytren’s cord with the goal of weakening and disrupting the cord. The day following the administration of Xiaflex®, force is applied to the area of contracture to further disrupt or actually break the fibrous band. Up to three injections may be provided to each affected cord at roughly one month intervals. If a patient has multiple cords only one may be injected each day. Because the injection should not be around neurovascular bundles or into the tendon, the injections are done without analgesics so that the patient may report any nerve related pain. However local anesthesia may be allowed for the physical force to be applied the day after injection.

Complications of collagenase clostridium histolyticum have been reported including tendon rupture, allergy to the enzyme, and nerve damage. The results are generally good with low recurrence rates at 2 to 4 years; but by 8 years post injection as many as 50% of people may have recurrence.

**Searches**

AmeriHealth Caritas searched PubMed and the databases of:

- UK National Health Services Centre for Reviews and Dissemination.
- Agency for Healthcare Research and Quality’s National Guideline Clearinghouse and other evidence-based practice centers.
- The Centers for Medicare & Medicaid Services (CMS).

We conducted searches on September 6, 2016. Search terms were: “Xiaflex®” and “collagenase clostridium histolyticum”.

We included:

- **Systematic reviews**, which pool results from multiple studies to achieve larger sample sizes and greater precision of effect estimation than in smaller primary studies. Systematic reviews use predetermined transparent methods to minimize bias, effectively treating the
review as a scientific endeavor, and are thus rated highest in evidence-grading hierarchies.

- **Guidelines based on systematic reviews.**
- **Economic analyses**, such as cost-effectiveness, and benefit or utility studies (but not simple cost studies), reporting both costs and outcomes — sometimes referred to as efficiency studies — which also rank near the top of evidence hierarchies.

**Findings**

N/A

**Policy updates:**

**Xiaflex® update:**


Added Xiaflex® as an approved treatment for Peyronie’s disease.

On December 6, 2013 the U.S. Food and Drug Administration today approved a new use for Xiaflex® (collagenase clostridium histolyticum) as the first FDA-approved medicine to treat men with bothersome curvature of the penis, a condition known as Peyronie’s disease.

The safety and effectiveness of Xiaflex® for the treatment of Peyronie’s disease were established in two randomized double-blind, placebo-controlled studies in 832 men with Peyronie’s disease with penile curvature deformity of at least 30 degrees. Participants were given up to four treatment cycles of Xiaflex® or placebo and were then followed 52 weeks. Xiaflex® treatment significantly reduced penile curvature deformity and related bothersome effects compared with placebo.

Peyronie’s disease is caused by scar tissue that develops under the skin of the penis. This scar tissue causes an abnormal bend during erection and can cause problems such as bothersome symptoms during intercourse. In some men, Peyronie's disease causes a significant bend or pain. This can prevent a man from having sex or might make it difficult to get or maintain an erection (erectile dysfunction). For many men, Peyronie's disease also causes stress and anxiety. The cause of Peyronie's disease isn't completely understood, but a number of factors appear to be involved.

It's thought Peyronie's disease generally results from repeated injury to the penis. For example, the penis might be damaged during sex, athletic activity or as the result of an accident. However, most
often, men do not recall specific trauma to the penis.

During the healing process, scar tissue forms in a disorganized manner, which might then lead to a nodule that you can feel or development of curvature. A treatment course for Peyronie’s disease consists of a maximum of four treatment cycles. Each treatment cycle consists of two Xiaflex® injection procedures (in which Xiaflex® is injected directly into the collagen-containing structure of the penis) and one penile modeling procedure performed by the health care professional.

Clinicaltrials.gov  NCT01685437- September 12, 2012, A Phase 3, Open-label Study of the Safety and Effectiveness of AA4500 Administered Twice Per Treatment Cycle for up to Four Treatment Cycles (2 x 4) in Men With Peyronie’s Disease. Updated March 24, 2015

Summary of clinical evidence:

<table>
<thead>
<tr>
<th>Citation</th>
<th>Content, Methods, Recommendations</th>
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| Hurst, NEJM (2009)        | Key points:
|                           | ● 308 patients with 20° or more contracture, received up to 3 injections spaced q 4 weeks
|                           | ● After Rx treatment group ROM improved from 43.9 to 80.7 degrees vs. from 45.3 to 49.5 degrees, P<0.001
|                           | ● 3 complications (2 tendon rupture and 1 complex regional pain) and 26 reached no contracture. |
| Heimer, J Hand Surg (2013)| Key points:
|                           | ● 1,080 treated joints, 623 achieved 5° or less contracture following initial treatment
|                           | ● At three years 35% had recurrence to 20° or more
|                           | ● Recurrence rate is comparable to reported surgical rates. But this was not a two-armed study, but was a comparison of study to literature reports. |
| Bainbridge, J Plast Surg hand surg. (2012) | Key points:
|                           | ● Study from coded descriptions on 1082 patients with Dupuytren’s of whom 39% had prior surgery.
|                           | ● Improvements comparable between those with previous surgery and those who had no prior surgery
|                           | ● Conclusion that prior surgery does not affect efficacy of Xiaflex® for recurrences |
| Black, J Am Acad Orthop Surg (2011) | Key points:
|                           | ● Review article, focusing on genetic and other predisposing conditions.
|                           | ● Review of impacts of surgery and less invasive treatments.
|                           | ● Neither surgical nor non-surgical care is curative |
| Goldstein GM et al. (2013) | Key points:
|                           | ● IMPRESS (Investigation for Maximal Peyronie’s Reduction Efficacy and Safety Studies) I and II examined the clinical efficacy and safety of collagenase clostridium histolyticum intralvesional
injections in subjects with Peyronie disease.

- Post hoc meta-analysis of IMPRESS I and II data revealed that men treated with collagenase C. histolyticum showed a mean 34% improvement in penile curvature, representing a mean ± SD -17.0 ± 14.8 degree change per subject, compared with a mean 18.2% improvement in placebo treated men, representing a mean -9.3 ± 13.6 degree change per subject (p <0.0001).
- The mean change in Peyronie disease symptom bother score was significantly improved in treated men vs men on placebo (-2.8 ± 3.8 vs -1.8 ± 3.5, p = 0.0037). Three serious adverse events (corporal rupture) were surgically repaired.
- MPRESS I and II support the clinical efficacy and safety of collagenase C. histolyticum for the physical and psychological aspects of Peyronie disease.
- http://www.ncbi.nlm.nih.gov/pubmed/23376148?dopt=Citation

Gelbard M, et al. (2012)  

**Key points:**

- Collagenase clostridium histolyticum is an investigational nonsurgical treatment for Peyronie disease. In this phase 2b, double-blind, randomized, placebo controlled study we determined the safety and efficacy of collagenase C. histolyticum and assessed a patient reported outcome questionnaire.
- Collagenase C. histolyticum treatment was well tolerated. We noted significant improvement in penile curvature and patient reported outcome symptom bother scores, suggesting that this may be a safe, nonsurgical alternative for Peyronie disease.

**Glossary**

**Aponeurotomy** - Involves the release of the aponeurosis. This may be performed as an open surgical procedure or as a minimally invasive procedure.

**Collagenase** - An enzyme capable of causing the hydrolysis of collagen and gelatin

**Contracture** - Shortening of the tendon or muscle because of intrinsic or extrinsic conditions.

**Related Policies:**

AmeriHealth Caritas Northeast Utilization Management Program Description

**References**

Professional society guidelines/other:

Food and Drug Administration(FDA )approves first drug treatment for Peyronie’s disease  
http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm377849.htm
NHSC Collagenase clostridium histolyticum (Xiapex) for Dupuytren's contracture at NIHR Horizon Scanning Centre, National Institute for Health and Care Excellence. 2012 

Peer-reviewed references:


Clinical trials:


CMS National Coverage Determinations (NCDs):

No NCDs identified as of the writing of this policy.

Local Coverage Determinations (LCDs):

**Commonly submitted codes**

Below are the most commonly submitted codes for the service(s)/item(s) subject to this policy. This is not an exhaustive list of codes. Providers are expected to consult the appropriate coding manuals and bill in accordance with those manuals.

<table>
<thead>
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<th>CPT Code</th>
<th>Description</th>
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<td>20527</td>
<td>Injection, enzyme (e.g., collagenase), palmar fascial cord (i.e. Dupuytren’s contracture)</td>
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<tr>
<td>26341</td>
<td>Manipulation, palmar fascial cord (i.e. Dupuytren’s cord), post-enzyme injection (e.g. Collagenase), single cord</td>
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<table>
<thead>
<tr>
<th>ICD-10 Code</th>
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<tr>
<td>M72.0</td>
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<td>J0775</td>
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