Clinical Policy Title: Xiaflex for Dupuytren’s contractures and Peyronie’s disease

Clinical Policy Number: 14.02.01

Effective Date: December 1, 2013
Initial Review Date: July 17, 2013
Most Recent Review Date: September 21, 2017
Next Review Date: September 2018

Related policies:

None.

ABOUT THIS POLICY: Select Health of South Carolina has developed clinical policies to assist with making coverage determinations. Select Health of South Carolina’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 Select Health of South Carolina when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state and federal laws and/or regulatory requirements, the plan benefits and/or state and federal laws and/or regulatory requirements shall control. Select Health of South Carolina’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. Select Health of South Carolina’s clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, Select Health of South Carolina will update its clinical policies as necessary. Select Health of South Carolina’s clinical policies are not guarantees of payment.

Coverage policy

Select Health of South Carolina considers the use of Xiaflex® (collagenase clostridium histolyticum) to be clinically proven and, therefore, medically necessary for Dupuytren’s contracture 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.
- Xiaflex is an alternative to surgery.
- Procedure is performed in the physician office by an appropriately trained physician (including hand surgeon, orthopedic surgeon, plastic surgeon, and general surgeon).

Select Health of South Carolina also considers the use of Xiaflex (collagenase clostridium histolyticum) to be clinically proven and therefore medically necessary when the following criteria are met:

- Males over age 18 with a diagnosis of Peyronie’s disease and a palpable penile plaque and curvature of 30 degrees or more
- No history of hypersensitivity to Xiaflex exists
Limitations:

All other uses of Xiaflex (collagenase clostridium histolyticum) are considered investigational/experimental and, therefore, not medically necessary.

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>
</tr>
</thead>
<tbody>
<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>
</tr>
<tr>
<td>• Health care sites must be certified with the program and ensure that Xiaflex is only dispensed for use by certified prescribers.</td>
</tr>
</tbody>
</table>

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

Alternative covered services:

Surgical treatment with release 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. The disorder, which typically affects only the ring finger and pinky of one hand, can limit the ability to open the hand and grasp large objects.

Prevalence of Dupuytren’s contracture is estimated at 3-6 percent (Ball, 2007). There are a number of associations with Dupuytren’s contracture such as male predominance, Northern European or Scandinavian ancestry, and age over 50. It may be found more commonly in people with diabetes, seizures, heavy smokers, or alcoholism. Dolmans and the German and Dutch Dupuytren Study groups have reported finding nine different loci involved in genetic susceptibility. However, causes are still unknown. Pain may be present, but it is not a hallmark and, when present, it may resolve over time spontaneously (Mayo, 2017).

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 on the total passive extension deficit:

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

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. Duration of the positive effect is unknown. For that reason, needle aponeurotomy is not considered a medically necessary service. Open and closed fasciectomy are used; open partial fasciectomy is the most commonly employed method (Chen, 2011). Of U.S. Dupuytren’s cases, the percent treated with fasciotomy or fasciectomy fell from 38 to 24 percent from 2007 to 2014, while those treated with Xiaflex injections rose from 0 to 11 percent (Lipman, 2017). The proportion of patients treated with minimally invasive techniques (Xiaflex and needle aponeurotomy) rose from 14 to 39 percent from 2007 to 2013 (Zhao, 2016).

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 considered a medically necessary service. The use of steroid injections provides short-term benefit with the reduction of pain and swelling.

**Xiaflex (collagenase clostridium histolyticum):**

In September 2009, Xiaflex received U.S. Food and Drug Administration (FDA) approval as a first-in-class orphan drug. It is a bacterial collagenase injected into the Dupuytren’s cord to weaken and disrupt 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 allow for physical force to be applied the day after injection.

Peyronie’s disease is a type of erectile dysfunction marked by a bend in the penis from fibrous scar tissue that causes painful erections. The cause of the condition is unknown, but speculation is that it results from repeated trauma to the penis. Over 90 percent of Peyronie’s cases are males over age 40. The main symptom of Peyronie’s is plaque, beneath the skin, on the upper side of the penis; in some cases, the plaque can be present around the entire penis. In cases of Peyronie’s, the penis tends to bend upwards during erections; cases where the bending is greater than 30 degrees is considered sufficient for treatment to commence (Kim, 2016). The prevalence of Peyronie’s has been estimated to be 7.3 percent (DeBenedetti, 2011).
Xiaflex was also approved by the FDA in December 2013 for Peyronie’s disease, making it the only medical treatment approved by the Administration (FDA, 2016).

searches

Select Health of South Carolina 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.
- Centers for Medicare & Medicaid Services (CMS).

We conducted searches on June 22, 2017. 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 pre-determined transparent methods to minimize bias, effectively treating the review as a scientific endeavor, and thus are rated highest in evidence grading hierarchies.
- Guidelines based on systematic reviews.
- Economic analyses, such as cost-effectiveness, 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

DUPUYTREN’S CONTRACTURES:

The American Academy of Orthopaedic Surgeons acknowledges the improvements observed by Xiaflex injections, while noting that studies of long-term outcomes are needed (AAOS, 2017).

Two studies known as Collagenase Option for the Reduction of Dupuytren’s (CORD I and CORD II) compared Xiaflex to placebo in 2,630 injections in hands of 1,082 persons with Dupuytren’s were the basis for the 2010 FDA approval of the drug. Both found a strongly significant reduction in contracture compared with placebo (Kaplan, 2011). Another study of 308 persons with Dupuytren’s from this early period found those given Xiaflex, compared to placebo, had a significantly greater rise in percent of collagen cords meeting primary endpoints (64.0 versus 6.8), as did degree increases in range of motion (36.8 versus 6.2) (Hurst, 2009). Another study of 66 Dupuytren’s patients receiving Xiaflex showed a greater reduction in contracture compared to placebo after 30 days (70.5 versus 13.6 percent), and a greater increase in average range of motion (35.4 versus 7.6 degrees) (Gilpin, 2010).
A systematic review of 191 articles found that recurrence rates for persons given Xiaflex (10, 12, 15, and 31 percent, by study) were significantly lower than for open partial fasciectomy (12, 27, 30, and 31), and needle aponeurotomy (50 and 58). For the one complication with comparable data, the skin tear rates for Xiaflex (9, 11, and 15 percent) were significantly lower than those of needle aponeurotomy (9, 16, and 25). The rate for open partial fasciectomy was just two percent, but only based on one study (Chen, 2011). Another systematic review of 43 studies found Xiaflex yielded better outcomes than did open fasciectomy, in a more cost-effective manner (Smeraglia, 2016).

Other studies document inferior results for Xiaflex compared to fasciectomy. A review of 142 patients found fasciectomy had a greater degree of correction than did Xiaflex (Muppavarapu, 2015). Another comparison of the two treatments followed 50 patients for two years; the clinical improvement was significantly higher (29 versus 7 percent) and complication rate was significantly lower (24 versus 93 percent) for fasciectomy patients (Skov, 2017).

A systematic review of 55 articles describes Xiaflex as “effective and immediate” but more costly than other treatments (Mafi, 2012).

The rate of adverse events, total and serious, reported for 5,400 injections was 5.0 and 0.6 percent, respectively, after one year (Peimer, 2012). A systematic review of 33 studies found the most common adverse events were peripheral edema (54.4 percent), bruising (42.9), and upper limb pain (28.3) (Sanjuan-Cervero, 2017).

In a review of 11 trials (n=1082) of Xiaflex and 48 trials (n=7727) of fasciectomy, Xiaflex had lower adverse event rates for nerve injury, neurapraxia, complex regional pain syndrome, and arterial injury; and higher rates for tendon injury, skin injury, and hematoma (Peimer, 2015). No differences in adverse event rates were found between high-risk groups (older, males, and diabetics) and all other groups (Raven, 2014).

Recurrence (at least 20 degrees worsening) after two years was 35 percent, comparable to other standard treatments for Dupuytren’s (Peimer, 2013).

Studies known as JOINT I and JOINT II, of 587 patients injected with Xiaflex, found an average 73 percent in contracture and an increase of 30 degrees in range of motion after 30 days (Witthaut, 2013). Another study reviewed effects of two concurrent Xiaflex injections into cords affecting two joints in the same hand, followed by a finger extension 24 hours later, on 60 subjects. Reduction in average total contracture was 76 percent (87 to 24 degrees) after 30 days, and both patient and provider satisfaction levels were high (Coleman, 2014).

A review of 422 patients with previous surgery for Dupuytren’s were given Xiaflex on the operating hand (n=206) and non-operating hand (n=196). There was no significant difference between groups in improvement of contracture or range of motion, and authors conclude that prior surgery does not affect
Xiaflex efficacy or safety (Bainbridge, 2012). Retreatment in 51 adult Dupuytren’s patients documented after one year that 57 percent achieved contracture under 5 degrees, and 86 percent had increased range of motion of at least 20 degrees (Bear, 2017).

Two simultaneous injections into the same hand has been shown to be effective in a multi-center study of 715 Dupuytren’s patients. After 30 days, average contracture fell from 98 to 27 degrees and average range of motion rose from 90 to 156 degrees; most adverse events were mild or moderate, and required no treatment (Gaston, 2015).

An economic evaluation of 30 trials, eight of which were randomized, found that Xiaflex for Dupuytren’s performed better than placebo. However, compared to limited fasciectomy, Xiaflex was more costly and yielded fewer quality of life years (Brazzelli, 2015).

PEYRONIE’S DISEASE:

Two guidelines on Peyronie’s disease treatment stated that Xiaflex injections could be given if the patient had curvature of greater than 30 degrees, and the physician counseled the patient on risks and benefits of the condition (Nehra, 2015; (NICE, 2015).

The major source behind approval of Xiaflex for Peyronie’s disease was two clinical trials known as Investigation for Maximal Peytonie’s Reduction Efficacy and Safety (IMPRESS). A review of the two studies (n=832) at 64 sites documented a 34 percent improvement in curvature for the treatment group, compared to just 18 percent (Gelbard, 2013).

A review of six studies analyzed adverse effects from Xiaflex treatments of Peyronie’s disease. Most (85.8 percent) of 1044 patients reported at least one adverse effect; of these, 82.7 percent reported penile bruising, and 75.2 percent had mild-to-moderate effects (Carson, 2015). A total of 79 percent of adverse effects resolve without additional therapy (Equi Rojo, 2014).

Limited evidence exists that other treatments may improve Peyronie’s symptoms. One study of 82 patients given 24 verapamil (calcium channel blocker) penile injections over 18 months, along with blueberries had an 81.5 percent improvement in curvature, significantly higher than an 8.1 percent improvement for those with no treatment (Paulis, 2013).

Policy updates:

A total of six clinical guidelines/other and 17 peer-reviewed references were added to, and one guideline/other and seven peer-reviewed references were removed from, this policy in 2017.

Summary of clinical evidence:
<table>
<thead>
<tr>
<th>Citation</th>
<th>Content, Methods, Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peimer (2015)</td>
<td>Key points:</td>
</tr>
<tr>
<td></td>
<td>• Comparison of 11 CCH trials (n=1082) and 48 fasciectomy trials (n=7727).</td>
</tr>
<tr>
<td></td>
<td>• CCH had lower adverse event rates for nerve injury, neuropraxia, complex regional pain syndrome, and arterial injury.</td>
</tr>
<tr>
<td></td>
<td>• CCH had higher adverse event rates for tendon injury, skin injury, and hematoma.</td>
</tr>
<tr>
<td>Heimer (2013)</td>
<td>Key points:</td>
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<tr>
<td></td>
<td>• Of 1,080 treated joints, 623 achieved 5° or less contracture following initial treatment.</td>
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<tr>
<td></td>
<td>• At three years, 35% had recurrence to 20° or more.</td>
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<tr>
<td></td>
<td>• Recurrence rate is comparable to reported surgical rates. But this was not a two-armed study; it was a comparison of study to literature reports.</td>
</tr>
<tr>
<td>Bainbridge (2012)</td>
<td>Key points:</td>
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<tr>
<td></td>
<td>• Study from coded descriptions on 1,082 patients with Dupuytren’s contracture, of whom 39% had prior surgery.</td>
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<tr>
<td></td>
<td>• Improvements were comparable between those with previous surgery and those who had no prior surgery.</td>
</tr>
<tr>
<td></td>
<td>• Conclusion: Prior surgery does not affect efficacy of Xiaflex for recurrences.</td>
</tr>
<tr>
<td>Chen (2011)</td>
<td>Key points:</td>
</tr>
<tr>
<td></td>
<td>• Systematic review of 191 articles on outcomes for Dupuytren’s patients</td>
</tr>
<tr>
<td></td>
<td>• Recurrence rates for CCH patients (10, 12, 15, and 31%) lower than open partial fasciectomy (12, 27, 30, 31) and needle aponeurotomy (50 and 58)</td>
</tr>
<tr>
<td></td>
<td>• Skin tear rates for CCH (9, 11, and 15%) were lower than needle aponeurotomy (9, 16, and 25); open partial fasciectomy data only exists for one study (2%)</td>
</tr>
<tr>
<td>Hurst (2009)</td>
<td>Key points:</td>
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<tr>
<td></td>
<td>• 308 patients with 20° or more contracture, received up to three injections spaced every four weeks.</td>
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<td></td>
<td>• After Rx treatment, group Range of Motion improved from 43.9 to 80.7 degrees versus from 45.3 to 49.5 degrees, P &lt; 0.001.</td>
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<tr>
<td></td>
<td>• Three complications (two tendon rupture and one complex regional pain) and 26 reached no contracture.</td>
</tr>
</tbody>
</table>

**References**

**Professional society guidelines/other:**


Peer-reviewed references:


Debenedetti DB, Nguyen D, Zografos L, Ziemiecki R, Zhou X. Prevalence, incidence, and treatments of


**CMS National Coverage Determination (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>
<tr>
<th>CPT Code</th>
<th>Description</th>
<th>Comment</th>
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<tbody>
<tr>
<td>20527</td>
<td>Injection, enzyme (e.g., collagenase), palmar fascial cord (i.e. Dupuytren’s contracture)</td>
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</tr>
<tr>
<td>26341</td>
<td>Manipulation, palmar fascial cord (i.e. Dupuytren’s cord), post-enzyme injection (e.g. Collagenase), single cord</td>
<td></td>
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<tr>
<td>54200</td>
<td>Injection procedure for Peyronie disease;</td>
<td></td>
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<tr>
<td>54201</td>
<td>Injection procedure for Peyronie disease; with surgical exposure of plaque</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>ICD-10 Code</th>
<th>Description</th>
<th>Comment</th>
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</thead>
<tbody>
<tr>
<td>M72.0</td>
<td>Dupuytren’s contracture</td>
<td></td>
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<tr>
<td>N48.6</td>
<td>Induration penis plastica</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>HCPCS Level II Code</th>
<th>Description</th>
<th>Comment</th>
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</thead>
<tbody>
<tr>
<td>J0775</td>
<td>Injection, collagenase clostridium histolyticum</td>
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</table>