Subject: Xiaflex (collagenase, clostridium histolyticum) for Peyronie Disease	**Original Effective Date:** 7/27/2016
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DISCLAIMER

This Molina Clinical Policy (MCP) is intended to facilitate the Utilization Management process. It expresses Molina's determination as to whether certain services or supplies are medically necessary, experimental, investigational, or cosmetic for purposes of determining appropriateness of payment. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered (i.e., will be paid for by Molina) for a particular member. The member's benefit plan determines coverage. Each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their providers will need to consult the member's benefit plan to determine if there are any exclusion(s) or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and a member's plan of benefits, the benefits plan will govern. In addition, coverage may be mandated by applicable legal requirements of a State, the Federal government or CMS for Medicare and Medicaid members. CMS's Coverage Database can be found on the CMS website. The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this MCP document and provide the directive for all Medicare members.

Contents

SUMMARY OF EVIDENCE/POSITION

This policy addresses **Xiaflex (collagenase clostridium histolyticum)** for treatment of adult men with **Peyronie disease** with a palpable plaque and curvature deformity of at least 30 degrees at the start of therapy when appropriate criteria are met.

*REFER to MCP-259 for Xiaflex (collagenase clostridium histolyticum) for the treatment of Dupuytren's contracture.

Peyronie disease (PD) is defined by the American Urological Association (AUA) as an acquired penile abnormality characterized by fibrosis of the tunica albuginea, which may be accompanied by pain, deformity, erectile dysfunction, and/or distress.

- PD is a fibrotic disease of the tunica albuginea of the penis that can result in penile curvature/deformity and sexual dysfunction. Angulation can occur from the collagen deposition. It may continue to progress and can approach a maximum of a 90-degree angle.
- The current prevalence of PD is approximately 5 percent in men. The true prevalence of PD may be underestimated as men might be reluctant to report a condition to their clinician due to emotional distress, and/or older men may accept the condition as a result of aging.

Xiaflex (collagenase clostridium histolyticum)

- The first FDA-approved medicine to treat men with bothersome curvature of the penis, a condition known as Peyronie disease. At the time of this writing (July 2016), collagenase is the only pharmacological treatment FDA approved for the treatment of Peyronie Disease.
- An injectable formulation of purified collagenase, an enzyme that causes collagen to degrade within the connective tissue. Collagenase C. histolyticum contains 2 forms of microbial collagenase (collagenase AUX-I and collagenase AUX-II) isolated and purified from the fermentation of C. histolyticum bacteria; collagenase lyses collagen, leading to enzymatic disruption of contracted Dupuytren cord or Peyronie plaque (both comprised primarily of collagen).[a] The signs and symptoms of Peyronie disease are caused by a collagen plaque (again comprised mostly of collagen); injection of Xiaflex can result in the enzymatic disruption of the plaque reducing curvature deformity and patient bother.[a]

- Optimal therapy has not been determined. Options for the management of PD include observation, medical, or surgical therapy, depending upon the severity of the disease. Observation is recommended in some patients whose pain/curvature are minimal and do not preclude normal sexual function.

- Pharmacologic treatments of PD typically include oral or intralesional drug therapy. Oral drug therapy include pentoxifylline, tamoxifen, colchicine, vitamin E and intralesional injections such as verapamil, interferon alpha 2b and collagenase clostridium histolyticum (the only FDA approved medication therapy for PD).[D]

The American Urological Association (AUA 2015) published a guideline addressing the treatment of PD: [A]

- AUA guidelines recommend oral NSAIDs for pain associated with PD. AUA states that oral vitamin E, tamoxifen, procarbazine, omega-3 fatty acids, or a combination of vitamin E with L-carnitine is not recommended to be utilized in stable PD.
- Intralesional collagenase with clinician/patient modeling is recommended in individuals stable PD, a curvature >30 and <90 degrees, and when the patient has intact erectile function (regardless of whether medications are needed to obtain erection or not). [3,A]
- Clinicians may administer intralesional collagenase clostridium histolyticum in combination with modeling by the clinician and by the patient for the reduction of penile curvature in patients with stable PD, penile curvature > 30 and < 90, and intact erectile function (with or without the use of medications). This recommendation is based on the findings of the IMPRESS studies and was given a "Moderate Recommendation" with an "Evidence Strength Grade B," indicating moderate quality evidence and moderate certainty.

The FDA review and approval were based on the results of safety and efficacy data from the pivotal IMPRESS (The Investigation for Maximal Peyronie Reduction Efficacy and Safety Studies) trials, the phase III double-blinded, placebo-controlled studies that assessed CCH for the treatment of PD. In IMPRESS I and IMPRESS II at 52 weeks, both co-primary endpoints met statistical significance for mean percent change in penile curvature deformity and mean change in the PDQ bother domain score for treated subjects versus placebo patients.

Summary

- The evidence for the use of clostridial collagenase in individuals with PD includes two randomized trials and several non-comparative studies.
- Relevant outcomes are symptoms, change in disease status, functional outcomes, and quality of life.
- Clostridial collagenase–treated subjects demonstrated significant improvements in penile curvature and reported improvements their degree of bother related to the disease. However, evidence demonstrating health outcome improvements is lacking and it is not clear that these improvements in curvature or in the degree of symptom bother translated into differences in patient outcomes, and whether the benefit of treatment exceeds the risks.
- 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.

FDA Indications

Peyronie disease: Treatment of adult men with Peyronie disease with a palpable plaque and curvature deformity of at least 30 degrees at the start of therapy.

- *Orphan drug designation: Treatment of Peyronie disease*

Dupuytren contracture: Treatment of adults with Dupuytren contracture with a palpable cord. **NOTE: This indication is not addressed in this coverage policy.** REFER to MCP-259 for Xiaflex (collagenase clostridium histolyticum) for the treatment of the treatment of adults with Dupuytren's contracture.

- *Orphan drug designation: Treatment of advanced (involutional or residual stage) Dupuytren disease*

Available as: Single-use glass vials containing 0.9 mg of collagenase clostridium histolyticum as a sterile, lyophilized powder for reconstitution

FDA Approved

February 2010: Dupuytren's contracture with a palpable cord

December 2013: Peyronie disease; Xiaflex is the first pharmaceutical approved for this indication.

Black Box Warnings: A Black Box Warning is noted from the FDA for corporal rupture (penile fracture) or other serious penile injury in the treatment of Peyronie disease.

Xiaflex Risk Evaluation and Mitigation Strategy (REMS) Program

REMS is a program to manage known or potential serious risks associated with a drug and is required by the Food and Drug Administration (FDA) to ensure that the benefits of the drug outweigh its risks. Xiaflex is available only through the Xiaflex REMS Program. Each indication has separate REMS requirements and educational material. Required components of the Xiaflex REMS Program include the following:

- Prescribers must be certified with the program by enrolling and completing training in the administration of Xiaflex treatment for the respective indication.
- Healthcare sites must be certified with the program and ensure that Xiaflex is only dispensed for use by certified prescribers.

CLASSIFICATION: Connective Tissue Agent; Enzyme; Proteolytic Enzyme; Tissue Permeability Modifier

COVERAGE CRITERIA FOR INITIAL AUTHORIZATION

Xiaflex (collagenase clostridium histolyticum) may be authorized for members who meet **ALL** of the following criteria **[ALL]**

1. Prescriber specialty [ALL]

- ❒ Prescribed by, or in consultation with, a board-certified urologist or specialist in the treatment of male urological diseases. Submit consultation notes if applicable.

- ❒ Prescriber is Xiaflex Risk Evaluation and Mitigation Strategy (REMS) certified[a]
  - *Xiaflex is only available through REMS program due to risk of serious adverse events. The Xiaflex REMS Program that requires prescribers to be certified with the program by enrolling and completing training in the administration of Xiaflex treatment. Healthcare sites must also be certified with the program and ensure that Xiaflex is only dispensed for use by certified prescribers when used for Peyronie disease.*
  - *The goal of the Xiaflex REMS training is to certify that the appropriate physicians and practice sites are trained in the use of the agent and to attempt to mitigate the serious risk of penile fracture (corporal rupture) and other serious injuries to the penis such as hematoma.*

2. Diagnosis/Indication [ALL]
Clinical **documented** diagnosis of (*includes clinical notes from the member's medical records including any applicable labs and/or tests, supporting the diagnosis*):

- ❒ Diagnosis of Peyronie disease with a palpable plaque

- ❒ Penile curvature **greater than or equal to 30 degrees** prior to treatment with the requested agent
  - *American Urological Association (AUA) Guideline (2015) states that intralesional collagenase with clinician/patient modeling is recommended when the patient has stable PD, a curvature >30 and <90 degrees, and when the patient has intact erectile function (regardless of whether medications are needed to obtain erection or not).*[A,3]

- ❒ Stable disease* (resolution of penile pain and no worsening curvature) **for at least 12 months**
  - *AUA Guideline (2015) states that intralesional collagenase with clinician/patient modeling is recommended when the patient has stable PD, a curvature >30 and <90 degrees, and when the patient has intact erectile function (regardless of whether medications are needed to obtain erection or not).*[A,3]

- ❑ Intact erectile function (with or without use of medications)
  - *AUA Guideline (2015) states that intralesional collagenase with clinician/patient modeling is recommended when the patient has stable PD, a curvature >30 and <90 degrees, and when the patient has intact erectile function (regardless of whether medications are needed to obtain erection or not).*[A,3]

3. Age/Gender/Other restrictions [ALL]

- ❒ 18 years of age or older
  - *The safety and effectiveness for use in children less than 18 years of age has not been established.*[a]

4. Step/Conservative Therapy/Other condition Requirements [ALL]

- ❒ An inadequate response, contraindication clinical intolerance, or other clinical rationale explaining the inappropriateness to the following alternative/conservative treatments. Documentation required. [ONE]
  - ❍ Verapamil (intralesional injection)[D]
  - ❍ Pentoxifylline[13,D,g]

5. Contraindications*/Exclusions/Discontinuations

Authorization will not be granted if ANY of the following conditions apply [ANY]

- ❒ Non-FDA approved indications
- ❒ Hypersensitivity to Xiaflex (collagenase clostridium histolyticum) or to collagenase used in any other therapeutic application or application method
- ❒ Peyronie plaques that involve the penile urethra

6. Labs/Reports/Documentation required [ALL]

All documentation for determination of medical necessity must be submitted for review. Prescriber to submit medical records and specific labs, chart notes, and documentation as indicated in the criteria above. Letters of support and/or explanation are often useful but are not sufficient documentation unless ALL specific information required by this MCP is included.

NOTE: Additional documentation, rationale, and/or supporting evidence may be requested for review as deemed necessary or appropriate by Molina Medical/Pharmacy staff.

REAUTHORIZATION /CONTINUATION OF THERAPY

Xiaflex (collagenase clostridium histolyticum) may be authorized for continuation of therapy if meet **ALL** of the following criteria are met: **[ALL]**

1. Initial Coverage Criteria

- ❑ Member currently meets ALL initial coverage criteria

2. Compliance

N/A

3. Labs/Reports/Documentation required [ALL APPLICABLE]

- ❒ Documented response to last treatment demonstrated by curvature improvement BUT curvature *remains greater than 15 degrees* (after most recent treatment cycle). Submit chart note documenting progress of all previous treatment cycles

  NOTE: If the curvature deformity is less than 15 degrees after the first, second or third treatment cycle, or if further treatment is no longer clinically, then subsequent treatment cycles are not considered medically necessary and will therefore not be covered.

4. Discontinuation of Treatment [ANY]

Discontinue treatment if ANY of the following conditions applies: [ANY]

- ❑ Intolerable adverse effects or drug toxicity
- ❑ Persistent and uncorrectable problems with adherence to treatment
- ❑ Poor response to treatment as evidenced by physical findings and/or clinical symptoms
- ❑ Contraindications/Exclusions to therapy
  - ❍ Non-FDA approved indications
  - ❍ Hypersensitivity to Xiaflex (collagenase clostridium histolyticum) or to collagenase used in any other therapeutic application or application method

<u>Exclusions</u> [ANY]

- ❒ Curvature deformity is less than 15 degrees after the first, second or third treatment cycle
  NOTE: If the curvature deformity is *less than* 15 degrees after the first, second or third treatment cycle, or if the health care provider determines that further treatment is not indicated, then subsequent treatment cycles are not considered medically necessary and no further treatment may be authorized.
- ❒ More than 4 treatment cycles have been authorized per plaque (each cycle consists of 2 Xiaflex injection procedures and one penile modeling procedure)
  NOTE: The safety of more than 1 treatment course (i.e., 4 treatment cycles) is not known.[a]

ADMINISTRATION, QUANTITY LIMITATIONS, AND AUTHORIZATION PERIOD

Consult the manufacturer's labeling for more detailed information on dosage and administration of this drug, cautions, precautions, contraindications, potential drug interactions, laboratory test interferences, and monitoring.

1. **Recommended Dosage [ALL]**

   Peyronie disease If more than 1 plaque is present, inject into the plaque causing the curvature deformity.

   - ❑ **Initial dosage** Inject 0.58 mg into a Peyronie plaque; repeat injection 1 to 3 days later. A penile modeling procedure should be performed 1 to 3 days after the second injection.
   - ❑ **Repeat dosages** Administer a second treatment cycle (two 0.58 mg injections 1 to 3 days apart, followed by a penile modeling procedure 1 to 3 days after the second injection) in approximately 6 weeks if needed (maximum, 4 treatment cycles [a total of 8 injection procedures and 4 penile modeling procedures]). Do not administer subsequent treatment cycles if the curvature deformity is less than 15 degrees after a treatment cycle or if the health care provider determines that further treatment is not indicated.

     NOTE: The safety of more than 1 treatment course (i.e., 4 treatment cycles) is not known.[a]

2. **Authorization Limit [ALL]**

   A treatment course consists of a maximum of 4 treatment cycles. Each treatment cycle consists of two Xiaflex injection procedures and one penile modeling procedure. The second Xiaflex injection procedure is performed 1 to 3 days after the first. The penile modeling procedure is performed 1 to 3 days after the second injection of the treatment cycle. The interval between treatment cycles is approximately six weeks. The treatment course consists of a maximum of 8 injection procedures and 4 modeling procedures.

   - ❒ Site: If more than 1 plaque is present, inject into the plaque causing the curvature deformity.[a]
   - ❒ Dosing: 0.58 mg into target area in Peyronie plaque
   - ❒ Authorization [ALL]
     - ❍ Two injections per plaque per 28 days
     - ❍ Duration of Authorization Period: 3 months
     - ❍ Maximum 4 treatment cycles (2 injections/cycle) at 28 day intervals PER PLAQUE
     - ❍ Quantity Limit: **One treatment course** which consists of a maximum of 4 treatment cycles (or a maximum of 8 injection procedures and 4 modeling procedures.) PER PLAQUE

3. **Route of Administration [ALL]**

   - ❒ Xiaflex (collagenase clostridium histolyticum) is considered a **provider-administered** medication and must be administered by a healthcare provider experienced in the treatment of male urological diseases, who has completed required training for use of Xiaflex in the treatment of Peyronie disease.
     - ◆ *As serious complications or damage may occur, Xiaflex should only be administered by a health care professional experienced with hand injections (for Dupuytren's contracture) or urologists (for Peyronie disease) who have received certification in the Xiaflex REMS Program.*
   - ❒ Refer to MHI Policy & Procedure (P&P): Specialty Medication Administration Site of Care Policy: MHI Pharm 11

COVERAGE EXCLUSIONS

This policy only addresses the indication of **Xiaflex (collagenase clostridium histolyticum)** for treatment of adult men with **Peyronie disease** with a palpable plaque and curvature deformity of at least 30 degrees at the start of therapy when appropriate criteria are met.

All other uses of Xiaflex (collagenase clostridium histolyticum) that are not an FDA-approved indication or not included in the 'Coverage Criteria' section of this policy are considered experimental/investigational or not a covered benefit of this policy. This subject to change based on research and medical literature, or at the discretion of Molina Healthcare.

BACKGROUND/SUMMARY

Peyronie disease (PD) 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. The exact etiology of PD is unknown; however a suspected etiology is trauma or repetitive microvascular injury to the erect penis in men with genetic susceptibility to localized fibrosis.[g, B,C] Current theories regarding the cause of PD suggest that a variety of factors may be involved, such as a traumatic event, sometimes related to sexual intercourse, the presence of genetic predisposition, or occurrence of abnormal wound healing, including involvement of transforming growth factor β-1 or other profibrotic factors.[11]

PD symptoms may occur in up to 13% of men in the United States based on statistical modeling of data from cross-sectional study based on a web-based survey of a large (n = 11,420) probability-based panel of research subjects representative of the full US population estimated the prevalence of PD to range from 0.5% (the percentage of surveyed subjects with PD diagnosis) to 13% (percentage with diagnosis, treatment, or penile symptoms of PD). 11,420 men in the United States were evaluated by web-based survey regarding presence of PD, treatments, and symptoms and it was concluded that the prevalence of PD ranged from 0.5% (with diagnosis) to 13% (with diagnosis, treatment, or symptoms).[11]

The goals of treatment with medication include reducing plaque formation and pain, as well as minimizing curvature of the penis.

Pharmacologic Agents/Conventional Therapy

Effective treatment options for PD are limited. Most historically available, minimally invasive treatments have neither substantial data from controlled trials showing efficacy nor FDA approval as safe and effective for the treatment of PD. Surgical intervention may correct curvature deformity, but is associated with complications such as penile shortening, ED, neurovascular injury, infection, and decreased sexual sensation.[B,C]

- There are three intralesional drug treatments that have shown efficacy in randomized trials: verapamil, interferon alpha-2b, and collagenase.[D]
  - Intralesional injection in conjunction with oral pentoxifylline has been recommended to treat PD patients with moderate deformity (30 to 90 degree curvature) and an intact erection. Xiaflex (collagenase clostridium histolyticum) is the only FDA-approved intralesional treatment for men with PD at the time of this writing.[D]

Intralesional verapamil is thought to influence fibroblast metabolism by increasing collagenase activity and concurrently decreasing collagen production.[D]

- A number of trials[14,16-19] (but not all[20]) have demonstrated improvement in symptoms and penile plaque/curvature with intralesional verapamil therapy.[D]
- In a systematic review including four prospective studies of patients with mild PD (including only one small randomized, placebo-controlled trial), verapamil showed some benefit in penile curvature, plaque size, and penile pain.[14] Verapamil injection is safe, well-tolerated, and commonly used as part of nonsurgical PD management.[D]

Pentoxifylline

The exact mechanism of action of pentoxifylline is not known. Pentoxifylline blocks TGF-β1-mediated inflammation, prevents deposition of collagen type I and acts as a nonspecific phosphodiesterase inhibitor. The evidence for pentoxifylline has been more robust than other oral agents, given a recent well-designed, double-blind, placebo-controlled trial demonstrating efficacy.[21]

Pentoxifylline reduces disease progression in men with early Peyronie disease[13,D] [Dynamed rating: level 1 (likely reliable) evidence][g]

- Based on randomized trial of 228 patients (mean age 51 years) with early chronic Peyronie disease were randomized to pentoxifylline sustained-release 400 mg vs. placebo twice daily for 6 months
- To analyze the safety and efficacy of pentoxifylline sustained-release treatment in patients with early chronic PD
- Intention-to-treat analysis included 97% who took ≥ 1 dose and had ≥ 1 assessment
- Disease progression was defined as increase in plaque volume, penile curvature, pain, and/or peak systolic velocity
- Comparing pentoxifylline vs. placebo
  - Overall, 36.9% of patients who received pentoxifylline sustained-release reported a positive response (objective improvement in plaque size and penile curvature) compared to only 4.5% in the placebo group
  - Disease progression in 11% vs. 42% ($p = 0.01$, NNT 4)
  - Pain during erection in 10.8% vs. 17.3% ($p = 0.07$, NNT 16)
  - Change in mean plaque area -28.6 mm^2 vs. +42.9 mm^2 ($p = 0.001$)
  - Change in objective penile curvature (ventral, dorsal, lateral) ranged from -20 to -40 degrees vs. +22 to +31 degrees ($p \leq 0.01$)
- Conclusion: Pentoxifylline sustained-release was moderately effective in reducing penile curvature and plaque volume in patients with early chronic PD. Further studies with different treatment regimens are needed to better elucidate the beneficial effects of pentoxifylline sustained-release in PD
- Adverse effects associated with pentoxifylline included nausea, vomiting, and dyspepsia

PIVOTAL TRIALS

The FDA approval of Xiaflex for Peyronie disease was based on two multicenter, randomized, double-blind, placebo- controlled phase 3 studies in 832 adult males (n=832) with Peyronie disease in the pivotal IMPRESS I and IMPRESS II trials, in which Xiaflex was compared with placebo.

IMPRESS [Investigation for Maximal Peyronie Reduction Efficacy and Safety Studies] I and II)

These 2 studies examined collagenase injections in 417 and 415 participants (n=832), respectively, through a maximum of 4 treatment cycles, each separated by 6 weeks (for up to 8 injections of 0.58 mg collagenase). The duration of each study was 52 weeks.[1,a]

The objective of these studies was to evaluate the safety and effectiveness of collagenase clostridium histolyticum (CCH) intralesional injections administered twice per treatment cycle for up to 4 treatment cycles in men with PD.[1,a]

Subjects

- Inclusion: All subjects had a penile curvature deformity of at least 30 degrees in the stable phase of Peyronie disease. Men were stratified by baseline penile curvature (30 to 60 vs. 61 to 90 degrees). Patients were randomized 2:1 to receive either CCH (0.58 mg) or placebo injections plus penile remodeling.
- Exclusions: Patients with ventral curvature deformity, isolated hourglass deformity, or a calcified plaque that may interfere with injection technique were excluded.

The subjects received up to four treatment cycles of Xiaflex or placebo (weeks 0, 6, 12, 18) and were followed for weeks 24-52. Patients were randomized in a 2:1 ratio to receive up to 4 treatment cycles of Xiaflex or placebo. Each treatment cycle consisted of 2 study drug injections administered 1 to 3 days apart, followed by a penile modeling procedure 1 to 3 days after the second injection of the treatment cycle. Treatment cycles were repeated at approximately 6-week intervals for a maximum of 3 cycles. Patients were advised to perform penile modeling procedures at home for 6 weeks after each treatment cycle. Up to 4 total modeling procedures were performed.

There were 2 co-primary end points, which measured the change from baseline to week 52:

- Percentage change in penile curvature deformity
- Change in Peyronie Disease Bother Domain (PDBD) Score from the Peyronie Disease Questionnaire (PDQ) from baseline to week 52.

Intent to treat analysis showed: at week 52 in study 1, the mean change in penial curvature deformity from baseline was -35% in the Xiaflex arm (n=199) compared with -17.8% in the placebo arm (n=104; difference, -17.2%; 95% CI, -26.7% to -7.6%; $p < 0.01$).

- Study 1: baseline mean curvaturein the Xiaflex arm was 48.8 degrees and 49.0 degrees in the placebo arm. After treatment the Xiaflex arm had a -35.0% change while the placebo arm had a -17.8% change ($p< 0.01$).
- Study 2: baseline mean curvaturein the Xiaflex arm was 51.3% and 49.6% in the placebo arm. After treatment the Xiaflex arm had a -33.2% change while the placebo arm had a -21.8% change ($p< 0.01$). Xiaflex significantly reduced patient-reported bother associated with Peyronie disease compared with placebo ($p<0.05$).

The most frequently reported complications (≥ 45%) in the collagenase-treated group included penile ecchymosis, penile swelling and penile pain. Six participants experienced treatment-related serious adverse events, including corporeal rupture in 3 cases and penile hematoma in the other 3 cases. The 3 corporeal ruptures and one hematoma were successfully repaired surgically. Of the 2 remaining penile hematomas, one case was successfully resolved without intervention and the other resolved with aspiration.

CONCLUSION: Data from the IMPRESS I and II studies were combined. Participants treated with collagenase injections showed a mean percent improvement in penile curvature abnormality of 34%, compared to 18% improvement in penile curvature in the placebo group; this change in curvature and the percent improvement in the collagenase group were significantly greater than in the placebo group (each $p < 0.0001$). The mean change in the PDQ symptom bother domain score was significantly improved in the collagenase group vs. the placebo group (-2.8 ± 3.8 vs. -1.8 ± 3.5, $p = 0.0037$).

Additionally, at week 52 in study 1, the mean change in the PDBD score from baseline was -2.8 in the Xiaflex arm and -1.6 in the placebo arm (difference, -1.2; 95% CI, -2.4 to -0.03; $p < 0.05$). Similarly, at week 52 in study 2, the mean change in penial curvature deformity from baseline was -33.2% in the Xiaflex arm (n=202) compared with -21.8% in the placebo arm (n=107; difference, -11.4%; 95% CI, -19.5% to -3.3%; $p < 0.01$). Additionally, at week 52 in study 2, the mean change in the PDBD score from baseline was -2.6 in the Xiaflex arm compared with -1.5 in the placebo arm (difference, -1.1; 95% CI, -2.1 to -0.002; $p < 0.05$). Improvement in penile curvature deformity and in PDBD score in both studies was numerically similar among the subgroups stratified by baseline degree of curvature deformity. No clinically relevant differences in the co-primary endpoints were observed on the basis of erectile dysfunction severity and phosphodiesterase type 5 inhibitor use at baseline.

Safety and tolerability data

In pivotal studies, most patients completed all 4 cycles of treatment (8 injections total), including 434 of 551 Xiaflex -treated men (78.8%) and 247 of 281 men who received placebo (87.9%). The majority of Xiaflex-treated men and those who received placebo (92% and 61%, respectively) experienced at least 1 adverse reaction (AE).[1,a]

The most common adverse reactions associated with use of Xiaflex for Peyronie disease include penile hematoma, penile swelling and penile pain

Most AEs were local events of the penis and groin and the majority were of mild or moderate severity. Of these events, 79% resolved without intervention within 14 days of the injection. The AE profile was similar after each injection; no cumulative effects were observed.[a,f]

In the Xiaflex group, 30 patients did not receive all injections because of an AE and 44 patients did not receive all injections because their penile curvature deformity was less than 15° after one of the treatment cycles. Additional reasons patients did not receive all injections included inability to attend visits, treatment refusal, and consent withdrawal.[a,f]

SYSTEMATIC REVIEWS

In 2007, Russell et al. conducted a systematic review of plaque injection therapy for PD, which included two studies of collagenase.[5] Both articles reported positive treatment outcomes. One study was rated according to the Oxford Centre for Evidence-Based Medicine criteria as level 2 (RCT with low power or <80% follow-up/retention or good-quality, randomized prospective cohort study) and the other level 4 (case series or poor-quality cohort or case-control study).

HAYES

A Health Technology Assessment was not available for Xiaflex (collagenase clostridium histolyticum) for Peyronie Disease at the time of this review in May 2020.

DEFINITIONS

Collagen: A fibrous protein found in connective tissue, bone, and cartilage.

Collagenase: An enzyme capable of causing the hydrolysis of collagen and gelatin

APPENDIX

N/A

CODING INFORMATION: THE CODES LISTED IN THIS CLINICAL POLICY ARE FOR INFORMATIONAL PURPOSES ONLY. LISTING OF A SERVICE OR DEVICE CODE IN THIS POLICY DOES NOT IMPLY THAT THE SERVICE DESCRIBED BY THIS CODE IS A COVERED OR NON-COVERED. COVERAGE IS DETERMINED BY THE BENEFIT DOCUMENT. THIS LIST OF CODES MAY NOT BE ALL INCLUSIVE AND INCLUSION OR EXCLUSION OF ANY CODES DOES NOT GUARANTEE COVERAGE. PROVIDERS SHOULD REFERENCE THE MOST UP-TO-DATE SOURCES OF PROFESSIONAL CODING GUIDANCE PRIOR TO THE SUBMISSION OF CLAIMS FOR REIMBURSEMENT OF COVERED SERVICES.

HCPCS	Description
J0775	Injection, collagenase, clostridium histolyticum, 0.01 mg

*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).

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Package Insert, FDA, Drug Compendia

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Clinical Trials, Definitions, Peer-Reviewed Publications

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Policy Developed Internal Peer Review: 10/13/2015. MCPC Chair, Sr. Medical Director of Policy; Medical Directors et al.	7/27/2016
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Annual Review* No coverage criteria changes with this annual review. Minor revisions, including clarification and addition of language, however no change to intent.	P&T Q3 2020

*Policy Revisions and Annual Reviews: All content, clinical evidence, coverage criteria, practice guidelines, appendices and reference sections were reviewed and revised with the most recent medical literature and available evidence for both 'Annual Reviews' and 'Revisions.' Revisions include notable content updates or revisions that which may have affected criteria or requires review by a practicing specialist, Peer Reviewer. The revisions noted below but may not be all-inclusive of all revised criteria and content in each policy; refer to MCP for all revisions and complete context.