Subject: Xiaflex (collagenase, clostridium histolyticum) for Peyronie Disease	**Original Effective Date:** 7/27/2016
Policy Number: MCP-279	**Revision Date(s):** 6/9/2021
Review Date(s): 9/19/2017, 9/13/2018; Q4 2019; Q3 2020, 6/29/21	
MCPC Approval Date: 9/19/2017, 9/13/2018; 6/9/2021	
P&T Approval Date: Q4 2019; Q3 2020	

Contents

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.

The intent of the policy is to ensure appropriate selection of patients for therapy based on product labeling, clinical studies, nationally recognized authoritative references, and current peer-reviewed scientific literature. Molina Healthcare reserves the right to update this policy and revise coverage criteria to include or omit any off-label condition(s) as necessary based on medical literature and clinical studies that may become available. The information outlined in the MCP includes but is not limited to a review of evidence-based information obtained from the following sources Evaluation of New and Existing Technologies (UM 10). This policy is intended to address coverage criteria that are appropriate for the majority of individuals/members with a particular disease, illness, or condition. Each member's unique clinical circumstances may warrant individual consideration, based on review of applicable medical records.

RECOMMENDATION

This policy addresses **Xiaflex [collagenase clostridium histolyticum (CCH)]** 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 the treatment of Dupuytren's contracture.

Molina Healthcare reserves the right to update this policy and revise coverage criteria to include or omit any off-label condition(s) as necessary based on medical literature and clinical studies that may become available.

DESCRIPTION OF PROCEDURE/SERVICE/PHARMACEUTICAL

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 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. The current prevalence of PD in men is around 5%, a figure that may be underestimated due to patient reluctance in reporting the condition to their clinician. Testing is usually not for diagnosis since it is usually based on history and physical examination; however, duplex ultrasound may be used to define vascular flow rates and extent of plaque calcification. The goals of treatment with medication include reducing plaque formation and pain, as well as minimizing curvature of the penis.

Pharmacologic treatments of PD typically include oral or intralesional drug therapy. Oral drug therapy includes pentoxifylline, tamoxifen, colchicine, vitamin E and intralesional injections such as verapamil, interferon alpha 2b and collagenase clostridium histolyticum (CCH). Optimal therapy has not been determined and effective treatment options for PD are limited. 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. Surgical intervention may correct curvature deformity, but is associated with complications such as penile shortening, ED, neurovascular injury, infection, and decreased sexual sensation. There are three intralesional drug treatments that have shown efficacy in randomized trials: verapamil, interferon alpha-2b, and collagenase.

Xiaflex (CCH) is the first FDA-approved pharmacological agent for the treatment of PD in adult men. FDA approval was based on the results of safety and efficacy data from the pivotal IMPRESS (The Investigation for Maximal Peyronie Reduction Efficacy and Safety Studies) trials. IMPRESS I and IMPRESS II are phase 3, double-blinded, placebo-controlled studies that assessed CCH for the treatment of PD with follow-up through 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. 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 PD are lacking. The evidence is insufficient to determine the effects of the technology on health outcomes.

FDA INDICATIONS

FDA-approved indication does not alone dictate coverage. Molina Clinical Policy may not recommend coverage for all FDA-approved indications. Please review this Policy in its entirety for indications covered by Molina Healthcare.

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

Dupuytren contracture: Treatment of adults with Dupuytren contracture with a palpable cord.
*This indication is not addressed in this policy. REFER to MCP-259 for this indication.

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

FDA Approved
February 2010: Dupuytren's contracture with a palpable cord
December 2013: PD; Xiaflex is the first pharmaceutical approved for this indication.

Black Box Warnings: Corporal rupture (penile fracture) or other serious penile injury in the treatment of PD

Risk Evaluation and Mitigation Strategy (REMS): The REMS program for the treatment of PD includes an Elements to Assure Safe Use, an Implementation System, and a timetable for REMS assessments that must be submitted to the FDA.

NOTE: The REMS program regarding Xiaflex for the treatment of Dupuytren contracture is no longer required.

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

COVERAGE CRITERIA FOR INITIAL AUTHORIZATION

Xiaflex 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 has completed the required REMS training for the use of Xiaflex in the treatment of PD
     - *Because of the risks of corporal rupture or other serious penile injury, Xiaflex is available for the treatment of PD only through the Xiaflex REMS Program*

2. **Diagnosis/Indication [ALL]**
   Documentation of ALL of the following criteria are required. May include chart notes from the member's medical records, relevant labs and/or tests, and other relevant clinical information.

   - ❒ Diagnosis of Peyronie disease with a palpable plaque

   - ❒ Penile curvature **greater than or equal to 30 degrees** prior to treatment with the requested agent
     - *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))(AUA 2015).*

   - ❒ Stable disease* (resolution of penile pain and no worsening curvature) **for at least 12 months**

   - ❒ Intact erectile function† (with or without use of medications)

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.*

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)
  - ❍ Pentoxifylline

5. Contraindications/Exclusions/Discontinuations

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

- ❒ Non-FDA approved indications
- ❒ Hypersensitivity to Xiaflex 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 documentation as indicated in the criteria above, including but not limited to chart notes, applicable lab values and/or tests, adverse outcomes, treatment failures, or any other additional clinical information or clinical notes from the member's medical records supporting the diagnosis. Letters of support and/or explanation are often useful but are not sufficient documentation unless ALL specific information required by this MCP are 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 may be authorized for continuation of therapy if meet **ALL** of the following criteria are met: **[ALL]**

1. 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.

2. 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
- ❒ Non-FDA approved indications
- ❒ Hypersensitivity to Xiaflex (CCH) or to collagenase used in any other therapeutic application or application method

Exclusions

- ❒ 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.

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]**
   - ❒ **Initial injection:** 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 injections:** 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. The safety of more than 1 treatment course (i.e. 4 treatment cycles) is not known.

2. **Authorization Limit [ALL]**

   - ❒ Injection site: If more than 1 plaque is present, inject into the plaque causing the curvature deformity.
   - ❒ 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

     *A treatment course consists of a maximum of 4 treatment cycles (2 Xiaflex injections and one penile modeling procedure per cycle); a maximum of 8 injection procedures and 4 modeling procedures. Injections are administered 1 to 3 days apart. 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 6 weeks

3. **Route of Administration [ALL]**
   - ❒ Xiaflex 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 PD.
     - ◆ *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 PD) 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

All other uses of Xiaflex (CCH) that are not an FDA-approved indication or not included in the 'Coverage Criteria' section of this policy is 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

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

IMPRESS [Investigation for Maximal Peyronie Reduction Efficacy and Safety Studies; IMPRESS I and II) 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. The studies evaluated the safety and effectiveness of CCH intralesional injections administered twice per treatment cycle for up to 4 treatment cycles in men with PD. Patients had a penile curvature deformity of at least 30 degrees in the stable phase of PD and 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. The trial did not enroll patients with ventral curvature deformity, isolated hourglass deformity, or a calcified plaque that may interfere with injection technique. Patients were randomized in a 2:1 ratio to receive up to four cycles (eight injections) of Xiaflex or placebo and were followed for weeks 24-52. Each treatment cycle consisted of 2 Xiaflex 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. Two co-primary end points measured the change from baseline to week 52 of penile curvature deformity and Peyronie Disease Bother Domain (PDBD) Score from the Peyronie Disease Questionnaire (PDQ). Data from the IMPRESS I and II studies were combined and men 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. The majority of Xiaflex-treated men and those who received placebo (92% and 61%, respectively) experienced at least 1 adverse reaction. 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 most frequently reported complications (≥45%) in the collagenase-treated group included penile ecchymosis, penile swelling and penile pain. 6 participants experienced treatment-related serious adverse events (including corporeal rupture in 3 cases and penile hematoma in the other 3 cases).

Russell et al. conducted a systematic review of plaque injection therapy for PD, which included two studies of collagenase. 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).

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

- 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).
- Clinicians may administer intralesional CCH 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.

DEFINITIONS

N/A

APPENDIX

N/A

CODING INFORMATION

The codes listed in this policy are for reference purposes only. Listing of a service or device code in this policy does not imply that the service described by this code is covered or non-covered. coverage is determined by the benefit document. this list of codes may not be all inclusive.

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

KEO JUNE 3, 2021

REFERENCES

Package Insert, FDA, Drug Compendia

Xiaflex (collagenase clostridium histolyticum) [prescribing information]. Malvern, PA: Endo Pharmaceuticals Inc; April 2021.

American Hospital Formulary Service (AHFS). Drug Information 2021. [STAT!Ref Web site]. Available at: http://online.statref.com. [via subscription only]

IBM Micromedex. DRUGDEX (electronic version). IBM Watson Health, Greenwood Village, Colorado, USA. Available at: https://www.micromedexsolutions.com/ (cited May 2021).

Drug Facts and Comparisons. Facts and Comparisons eAnswers [online]. Clinical Drug Information LLC, 2021. Available from Wolters Kluwer Health, Inc. Accessed May 2021. [Available via subscription]

Clinical Pharmacology powered by ClinicalKey. Tampa (FL): Elsevier. c2016- [cited 2016 April 4]. Available at: http://www.clinicalkey.com. Accessed May 2021. [Available via subscription]

DynaMed [Internet]. Ipswich (MA): EBSCO Information Services. 1995 - . Record No. T113775, Peyronie Disease; [updated 2018 Nov 30, cited May 2021]. Available from https://www.dynamed.com/topics/dmp~AN~*T113775*. [Available via subscription]

Clinical Trials, Definitions, Peer-Reviewed Publications

Brant WO, Dean RC, Lue TF: Treatment of Peyronie disease with oral pentoxifylline. *Nat. Clin. Pract. Urol.*3(2),111–115 (2006).

Carson CC, 3rd, Sadeghi-Nejad H, Tursi JP, et al. Analysis of the clinical safety of intralesional injection of collagenase Clostridium histolyticum (CCH) for adults with Peyronie disease (PD). BJU Int. Nov 2015;116(5):815-822. PMID 25818264

Gelbard M, Goldstein I, Hellstrom WJ, et al. Clinical efficacy, safety and tolerability of collagenase clostridium histolyticum for the treatment of peyronie disease in 2 large double-blind, randomized, placebo-controlled phase 3 studies. *J Urol*. 2013 Jul; 190(1):199-207. PMID 23376148

Gelbard M, Hellstrom WJ, McMahon CG, et al. Baseline Characteristics from an Ongoing Phase 3 Study of Collagenase Clostridium Histolyticum in Patients with Peyronie Disease. *J Sex Med.* 2013 Sep 24.

Levine LA, Cuzin B, Mark S, et al. Clinical safety and effectiveness of collagenase clostridium histolyticum injection in patients with Peyronie disease: a phase 3 open-label study. The journal of sexual medicine. Jan 2015;12(1):248-258. PMID 25388099

Nguyen HMT, Yousif A, Chung A, et al. Safety and Efficacy of Collagenase Clostridium histolyticum in the Treatment of Acute Phase Peyronie's Disease: A Multi-institutional Analysis. Urology 2020; 145:147.

Russell S, Steers W, McVary KT. Systematic evidence-based analysis of plaque injection therapy for Peyronie disease. Eur Urol. Mar 2007; 51(3):640-647. PMID 17092631

Safarinejad MR, Asgari MA, Hosseini SY, Dadkhah F: A double-blind placebo-controlled study of the efficacy and safety of pentoxifylline in early chronic Peyronie disease. BJU Int.106(2),240–248 (2009).

Stuntz, M., Perlaky, A., des Vignes, F., Kyriakides, T., & Glass, D. (2016). The Prevalence of Peyronie Disease in the United States: A Population-Based Study. *PLoS ONE*, *11*(2), e0150157. http://doi.org/10.1371/journal.pone.0150157

Yang KK, Bennett N. Peyronie's Disease and Injectable Collagenase Clostridium histolyticum: Safety, Efficacy, and Improvements in Subjective Symptoms. Urology 2016; 94:143.

Ziegelmann MJ, Viers BR, McAlvany KL, et al. Restoration of Penile Function and Patient Satisfaction with Intralesional Collagenase Clostridium Histolyticum Injection for Peyronie's Disease. J Urol 2016; 195:1051.

Professional Society Guidelines

American Urological Association (AUA)

- Nehra A, Alterowitz R, Culkin DJ, et al: American Urological Association Education and Research, Inc., Peyronie Disease: AUA Guideline. J Urol. 2015; 194(3):745-753.

European Association of Urology (EAU). EAU Guidelines on Penile Curvature. EAU website. www.uroweb.org/guidelines/ . EAU Guidelines. Edn. presented at the EAU Annual Congress Barcelona 2019. Available at: http://uroweb.org/guidelines/compilations-of-all-guidelines/ Accessed May 2021

Other Resources

UpToDate. Retrieved from www.uptodate.com [via subscription]

- Peyronie disease: Diagnosis and Medical Management. Topic last updated: Jan 29, 2021. Accessed May 2021

Policy History	Approval
Policy Developed Internal Peer Review: 10/13/2015. MCPC Chair, Sr. Medical Director of Policy; Medical Directors et al.	7/27/2016
Reviewed: 12/15/2016; 9/19/2017; 7/10/2018; Q4 2019 (P&T)	
Annual Review* No changes to medical necessity criteria. Minor revisions, including clarification and addition of language, however no change to intent.	P&T Q3 2020
Annual Review* In the 'Reauthorization/Continuation of Therapy' section, removed criterion for 1) Member currently meets ALL initial coverage criteria, and deleted the 'Compliance' criteria that stated "Not applicable or N/A"	MCPC 6/9/2021

**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.*