Molina Clinical Policy
Xiaflex for for Peyronie Disease
Policy No. 279

Last Approval: 6/9/2021
Next Review Due By: June 2022

DISCLAIMER

This Molina Clinical Policy (MCP) is intended to facilitate the Utilization Management process. Policies are not a supplementation or recommendation for treatment; Providers are solely responsible for the diagnosis, treatment and clinical recommendations for the Member. 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 (e.g., 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 and provide the directive for all Medicare members. References included were accurate at the time of policy approval and publication.

OVERVIEW

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 (Stuntz et al. 2016). 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 (collagenase clostridium histolyticum; 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.

COVERAGE POLICY

Xiaflex (collagenase clostridium histolyticum) for treatment of Peyronie disease **may be considered medically necessary** when **ALL** of the following clinical criteria are met:

1. Diagnosis of Peyronie disease with a palpable plaque; **AND**

2. Penile curvature deformity of at least 30 degrees at baseline (prior to use of Xiaflex); **AND**

3. Stable disease (resolution of penile pain and no worsening curvature) for at least 12 months; **AND**

4. Intact erectile function (with or without use of medications)
   Informational Note: 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).

AND

5. An inadequate response, contraindication clinical intolerance, or other clinical rationale explaining the inappropriateness to the following alternative/conservative treatments:
   a. Verapamil (intralesional injection)
   b. Pentoxifylline

CONTINUATION OF THERAPY

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.

LIMITATIONS AND EXCLUSIONS

The following are considered **contraindications/exclusions** based on insufficient evidence:

1. Hypersensitivity to Xiaflex (CCH) or to collagenase used in any other therapeutic application or application method
2. Treatment of Peyronie plaques that involve the penile urethra

Exclusions

1. 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.
2. Member previously been treated with a complete course (8 injections) of Xiaflex for Peyronie's disease
   NOTE: The safety of more than one treatment course (i.e., 4 treatment cycles) is not known.

The following are considered conditions for **discontinuation of treatment** and re-treatment may not be authorized:

1. Unacceptable adverse events, complications, or toxicity
2. Persistent and uncorrectable problems with adherence to treatment
3. Limited response to treatment as evidenced by physical findings and/or clinical symptoms

The following are considered **experimental, investigational and unproven** based on insufficient evidence:

1. Any indications other than those listed above

PRESCRIBER REQUIREMENTS: Prescribed by, or in consultation with, a board-certified urologist or specialist in the treatment of male urological diseases. Submit consultation notes if applicable; **AND**
Prescriber has completed the required REMS training for use of Xiaflex in the treatment of PD
Due to the risks of corporal rupture or other serious penile injury, Xiaflex is available only through the Xiaflex REMS Program

AGE RESTRICTIONS: 18 years of age or older

DOSING CONSIDERATIONS:
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.**

DURATION AND QUANTITY LIMITATIONS:
1. Initial authorization: One treatment cycle (2 Xiaflex injections and one penile modeling procedure per cycle)
2. Reauthorization: Up to 3 additional treatment cycles (6 Xiaflex injections and 3 penile modeling procedure per cycle)
3. Total authorization: ONE course of treatment per plaque; consists of a maximum of 4 treatment cycles (2 Xiaflex injections and one penile modeling procedure per cycle); total of 8 injection procedures and 4 modeling procedures.

ADMINISTRATION:
1. Xiaflex is considered a provider-administered procedure performed in a physician's office 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.
2. Refer to MHI Policy & Procedure (P&P): Specialty Medication Administration Site of Care Policy: MHI Pharm 11

DOCUMENTATION REQUIREMENTS. Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

DRUG INFORMATION

ROUTE OF ADMINISTRATION: Intralesional injection

DRUG CLASS: Connective Tissue Agent; Enzyme; Proteolytic Enzyme; Tissue Permeability Modifier

FDA-APPROVED USES:
- Peyronie Disease (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 DC with a palpable cord. *This indication is not addressed in this policy. REFER to MCP-259.

COMPENDIAL APPROVED OFF-LABELED USES: None

SUMMARY OF MEDICAL EVIDENCE

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).

National and Specialty Organizations

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.

SUPPLEMENTAL INFORMATION

Collagen: A fibrous protein found in connective tissue, bone, and cartilage.
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.
Fascia: A sheet of fibrous tissue that envelops the body beneath the skin; it also encloses muscles and groups of muscles and separates their several layers or groups.
Fasciectomy: Surgical removal of the fibrous tissue beneath the skin.
Fibroproliferative: Producing new fibrous tissue.
Metacarpophalangeal (MP) joint: Commonly referred to as the knuckle; attached to the proximal first phalanges.
Proximal interphalangeal (PIP) joint: The second joint of the finger.

CODING & BILLING INFORMATION

CPT	Description

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

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

CODING DISCLAIMER. Codes listed in this policy are for reference purposes only and may not be all-inclusive. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement. Listing of a service or device code in this policy does guarantee coverage. Coverage is determined by the benefit document. Molina adheres to Current Procedural Terminology (CPT®), a registered trademark of the American Medical Association (AMA). All CPT codes and descriptions are copyrighted by the AMA; this information is included for informational purposes only. Providers and facilities are expected to utilize industry standard coding practices for all submissions. When improper billing and coding is not followed, Molina has the right to reject/deny the claim and recover claim payment(s). Due to changing industry practices, Molina reserves the right to revise this policy as needed.

APPROVAL HISTORY

6/9/2021 MCPC	Policy reviewed. Updated references. No changes to medical necessity criteria. Updates to policy in Continuation of Therapy' section: Removal of criterion for 'Member currently meets ALL initial coverage criteria' and 'Compliance' criteria since not applicable to policy (states 'Not Applicable')
Q3 2020 P&T	Policy reviewed and updated, no changes in coverage criteria, updated references.
Q4 2019 P&T	Policy reviewed and updated, no changes in coverage criteria, updated references.
7/10/2018 MCPC	Policy reviewed and updated, no changes in coverage criteria, updated references.
9/19/2017 MCPC	Policy reviewed and updated, no changes in coverage criteria, updated references.
12/15/2016 MCPC	Policy reviewed and updated, no changes in coverage criteria, updated references.
7/27/2016 MCPC	New policy. Internal Peer Review. MCPC Chair, Sr. Medical Director of Policy and Medical Directors

REFERENCES

Government Agency
Centers for Medicare & Medicaid Services (CMS). Medicare Coverage Database. National Coverage Determination (NCD) Search. Accessed at: CMS ; CMS NCD

Prescribing Information and 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]. Accessed April 2021. Available at: http://online.statref.com. [via subscription only].

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

Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; 2021. Available at: http://www.clinicalpharmacology.com. Accessed April 2021. [via subscription]

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. Available at: http://doi.org/10.1371/journal.pone.0150157 Accessed May 2021

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.

National and Specialty Organizations

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 Peer Reviewed and Professional Organization Publications (used in the development of this policy)

UpToDate. Peyronie disease: Diagnosis and Medical Management. Topic last updated: Jan 29, 2021. Accessed May 2021 Retrieved from www.uptodate.com [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]

APPENDIX

Reserved for State specific information *(to be provided by the individual States, not Corporate). Information includes, but is not limited to, State contract language, Medicaid criteria and other mandated criteria.*