

Subject: Xiaflex (collagenase, clostridium histolyticum) for Dupuytren's Contracture	Original Effective Date: 10/13/2015
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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.

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)** for the treatment of **the treatment of adults with Dupuytren's contracture with a palpable cord** when appropriate criteria are met.

*Refer to MCP-279 for the treatment of Peyronie Disease.

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

Dupuytren contracture (DC) is a progressive, nonmalignant fibroproliferative disorder that affects the palmar and digital fascia of the hand and results in contracture deformities. It is characterized by the abnormal production of collagen nodules, which often develop into cords that connect the dermis to the palmar fascia, causing affected joints to bend or flex toward the palm in a constant state of contracture that limits finger movement and hand function. The joints commonly affected by DC are the metacarpophalangeal joints and the proximal interphalangeal joints, the fourth and fifth digits (ring and pinky). The exact etiology is unknown. The condition is more common in men, usually presenting in patients over the age of 50. Other potential risk factors include manual labor with vibration exposure, prior hand trauma, alcoholism, smoking, diabetes mellitus, hyperlipidemia, Peyronie disease, and complex regional pain syndrome (Hindocha et al.). Diagnosis is made clinically by thorough history and physical examination. Imaging (i.e. ultrasound, MRI, or CT scan) is usually not indicated unless diagnosis is uncertain or required to help rule out other pathology. The symptoms of DC are generally not painful unless aggravated by forceful activities that put pressure on the nodule. As the condition progresses, the cords of fibrous tissue form in the palm and run into the fingers or thumb, eventually, pulling into a permanently flexed position. The aggressive form of the disease can be debilitating, limiting the ability to perform everyday activities.

Treatment for DC is not curative, and the goals of treatment are to improve flexibility of the fingers and to evaluate the need for surgery or other interventions. Non-surgical and surgical options are available for management of DC and the choice of therapy mostly depends on the severity of disease, degree of deformity, limitations in function, and provider preference. Non-surgical options in the early stages include physical or occupational therapy, triamcinolone acetonide injections, collagenase injections, needle fasciotomy (needle aponeurotomy), and radiation therapy. Surgery is treatment of choice for advanced stages of disease and usually considered when disease is functionally symptomatic, or contracture is progressing. Surgical procedures include open excision (limited or total fasciectomy), open or percutaneous division (fasciotomy), or percutaneous puncture (needle aponeurotomy) of the culprit cord(s). There is no formal consensus though it is generally accepted that surgical procedures are reserved for patients with contractures >30 to 40 degrees at the metacarpophalangeal (MCP) or >20 degrees at the proximal interphalangeal (PIP) joint have been suggested as indications for surgery (Feldman et al. 2017; UTD 2021)

Xiaflex [collagenase clostridium histolyticum; (CCH)] is a bacterial collagenase injected into the Dupuytren's cord with the goal of weakening and disrupting the cord, which results in contracture reduction and range of motion improvement. Xiaflex contains purified collagenase clostridium histolyticum, consisting of two microbial collagenases, Collagenase AUX-1 and Collagenase AUX-II, which are isolated and purified from the fermentation of *Clostridium histolyticum* bacteria. Collagenases are proteinases that hydrolyze collagen in its native triple helical conformation under physiological conditions, resulting in lysis of collagen deposits. Xiaflex is the first FDA-approved non-surgical option for the treatment of adult patients with DC with a palpable cord. Xiaflex is indicated for the treatment of DC with a palpable cord, a condition involving the connective tissue in the hands that leads to abnormal curvature/contracture of the fingers.

FDA INDICATIONS

Dupuytren contracture: Treatment of adults with Dupuytren contracture with a palpable cord.

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.

*This indication is not addressed in this policy. REFER to MCP-279 for this indication.

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

FDA Approved: February 2, 2010

- ◆ *In February 2010, the FDA approved Xiaflex for treatment of adult patients with DC with a palpable cord. The FDA labeling states that up to 3 injections at 4-week intervals may be given into a palpable Dupuytren's cord with a contracture of a metacarpophalangeal joint or a proximal interphalangeal joint.*
- ◆ *In October 2014, FDA approved labeling for Xiaflex stated that up to two cords in the same hand may be injected at a single treatment visit.*

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

Risk Evaluation and Mitigation Strategy (REMS): The FDA-approved 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 (collagenase clostridium histolyticum) may be authorized for members who meet **ALL** of the following criteria [ALL]

1. Prescriber specialty [ONE]

- Prescribed and administered by a board-certified healthcare provider experienced in injection procedures of the hand and in the treatment of DC (i.e. board-certified hand surgeon, orthopedic surgeon, rheumatologist, or plastic surgeon).
- Prescriber has completed the required REMS training for use of Xiaflex in the treatment of DC
 - ◆ *Because of the risks of corporal rupture or other serious penile injury, Xiaflex is available for the treatment of DC only through the Xiaflex REMS Program*

2. Diagnosis/Indication [ALL]

Documentation of ALL 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 Dupuytren's contracture with a palpable cord
- A positive "tabletop test" (defined as the inability to simultaneously place the affected finger and palm flat against a tabletop)
- Documentation of ONE of the following: [ONE]
 - Flexion contracture > 20 degrees at the metacarpophalangeal (MP) joint
 - Flexion contracture > 20 degrees at the proximal interphalangeal (PIP) joint

Informational Note: Patients in clinical trials must have had a finger flexion contracture with a palpable cord of at least one finger (other than the thumb) of 20° to 100° in a metacarpophalangeal joint or 20° to 80° in a proximal interphalangeal (PIP) joint.

- Functional impairment as a result of the contracture

3. Age/Gender/Other restrictions

- 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]

- Member has **NOT** received a surgical treatment (e.g. fasciectomy, fasciotomy) on the selected primary joint within 90 days before the first injection
- Member has **NOT** received an anticoagulation medication (except for up to 150 mg/day of aspirin) within 7 days before the first injection

5. Contraindications*/Exclusions/Discontinuations

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

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

Exclusions

- Greater than 3 injections per cord
- Surgery on the primary joint within the past 90 days
- Concomitant use of anticoagulants and in patients with coagulation disorders is not recommended

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

1. Initial Coverage Criteria

- Reauthorization request is for treatment of a previously treated cord following recurrence:
Member currently meets ALL initial coverage criteria AND member has received less than 3 injections total per cord at 4-weeks apart
- For treatment of a new cord, submit new request for initial authorization

2. Compliance

- Member must follow-up within 24 hours following an injection for finger extension procedure if a contracture persists in order to qualify for more injections. **If after the second injection there is no improvement the 3rd injection may not be authorized.**

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

- Injection may be repeated up to a **maximum of 3 sessions per cord** (at 4-week intervals) IF:
Reduction in contracture of the selected primary joint (MP or PIP) is NOT within 0° to 5° of normal full extension. Documentation required.
NOTE: If there is no improvement after the 2nd second injection, the 3rd injection will NOT be authorized.

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 (CCH) or to collagenase used in any other therapeutic application or application method

Exclusions

- Greater than 3 injections per cord
- Surgery on the primary joint within the past 90 days
- Concomitant use of anticoagulants and in patients with coagulation disorders
- No improvement* after the 2nd injection then 3rd injection will NOT be authorized

**Improvement is defined as a reduction in contracture of the selected primary joint (MP or PIP) within 0° to 5° of normal full extension*

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]

- 0.58 mg intralesionally per cord affecting a MP joint or a PIP joint. If a contracture persists, finger extension procedure should be performed 24-72 hours following injection to facilitate cord disruption.
- If MP or PIP contracture remains, may re-inject cord with a single dose of 0.58 mg 4 weeks following initial injection
- Injections and finger extension procedures may be administered and performed up to **3 times per cord** at approximately 4-week intervals.
- Up to 2 injections per hand may be used during a treatment; 2 palpable cords affecting 2 joints or 1 palpable cord affecting 2 joints in the same finger may be injected at 2 locations during a treatment. Other palpable cords with contractures of MP or PIP joints may be injected at other treatment visits 4 weeks apart.

2. Authorization Limit [ALL]

- Injection Site: MP joint contractures or a PIP joint contractures
- Quantity limit: [ALL]
 - Initial authorization: One (1) time at no less than 4-week intervals
 - Reauthorization: One (1) time at no less than 4-week intervals; up to 2 additional times per cord (Total: 3 injections each affected cord at one-month intervals)
 - Total authorization: **Maximum of three (3) injections per cord** [One injection per 30 days]
- Duration of therapy: [ALL]
 - Injections and finger extension procedures may be administered up to 3 times per cord at approximately 4-week intervals [**3 injections per cord at 4-week intervals (maximum 12 weeks)**]
 - Repeat injection of a previously treated cord that has received the maximum of three (3) injections per cord will not be authorized
- Injections should be administered at no less than 4-week intervals

3. Route of Administration [ALL]

- ❑ Xiaflex is considered **provider-administered** medication and should be administered by a healthcare provider experienced in injection procedures of the hand and in the treatment of patients with Dupuytren's contracture. This procedure is followed-up with manipulation/stretching of the involved cord 24 hours after the injection unless the cord has ruptured. Each injection contains 0.58 mg of Xiaflex, must be performed in a **physician's office**.

- ❑ Refer to MHI Policy & Procedure (P&P): Specialty Medication Administration Site of Care Policy: MHI Pharm 11

COVERAGE EXCLUSIONS

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.

SUMMARY OF CLINICAL EVIDENCE

FDA approval of CCH for the management of Dupuytren contracture was based on the results of CORD I and CORD I Extension, multicenter, randomized, double-blind, placebo-controlled trials (n=374).

Hurst et al. (2009) conducted a double-blind, placebo-controlled, multicenter trial of 308 subjects with Dupuytren's joint contractures of 20 degrees or more to receive up to 3 injections of CCH (n=204) or placebo (n=104) in the contracted collagen cord at 30-day intervals, with manipulation of the joints the day following injection. Joints were stratified according to joint type (MP or PIP) and the joints were manipulated one day after injection if necessary. The mean number of affected joints was 3. The proportion of patients who had undergone prior surgery for DC was 38%, with 8% having had surgery for contracture on the same finger as the primary treated joint. Findings included a reduction in contractures to less than 5° in 64% of collagenase-injected patients compared with 6.8% of patients treated with placebo. Patients with MCP involvement tended to improve to a greater extent, as did those patients with less severe flexion contractures. The mean range of motion in the treated joints also improved significantly (from 44 to 81 degrees versus 45 to 50 degrees). Response rates were better in patients with less severe contractures (Hurst et al. CORD I Study Group).

Study 2 enrolled 66 patients (n=66). The mean number of affected joints was 3.3. The proportion of patients who had undergone prior surgery for DC was 53%, with 18% having had surgery for contracture on the same finger as the primary treated joint. More collagenase-treated joints achieved a reduction in contracture and a greater increase in range of motion of the affected joints.

Peimer et al. (2015) analyzed the recurrence rate of DC 5 years after successful treatment with CCH (CORDLESS study) in a non-interventional follow-up in patients from previous CCH clinical studies. Successfully treated joints was defined as joint correction 5° contracture or less following CCH treatment (prospectively established definition of success by Hurst et al.). The aim of this study was to evaluate the long-term durability of CCH treatment across multiple studies that used this definition of success. Recurrence was defined as 20° or greater worsening (relative to day 30 after the last injection) with a palpable cord or any medical/surgical intervention to correct new/worsening contracture. The study enrolled patients (n=644) with a total of 1,081 treated joints evaluated annually for contracture and safety at 2, 3, 4, and 5 years after their first injection (0.58 mg) of CCH. A total of 1,081 treated joints with more than one follow-up were analyzed; of these, 623 joints (58%) were initially treated successfully (i.e., reduction of contracture to 0° to 5°). The follow-up study concluded that longer-term (>5 years) follow-up in 1,081 joints treated with collagenase demonstrated an overall recurrence rate of 47% in both metacarpophalangeal and proximal interphalangeal joints combined. This rate (47%) is comparable with the published recurrence rates after surgical treatments, with one reported long-term treatment-related adverse event. The recurrence rate was worse at the PIP joint (66%) than the MCP joint (39%), which parallels results seen with needle aponeurotomy and open surgery (Peimer et al. 2015).

DEFINITIONS

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 called the knuckle, is attached to the proximal first phalanges.

Proximal interphalangeal (PIP) joint: The second joint of the finger.

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

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Policy History	Approval
<u>Policy Developed</u> Internal Peer Review: 10/13/2015. MCPC Chair, Sr. Medical Director of Policy.	MCPC 10/13/2015
<u>Annual Review*</u> 12/15/2016; 9/19/2017; 7/10/2018; Q4 2019 (P&T)	P&T Q4 2019
<u>Annual Review*</u> No coverage criteria changes with this annual review.	P&T Q3 2020
<u>Annual Review*</u> No changes to medical necessity criteria. Minor revisions, including clarification and addition of language, however no change to intent. In initial authorization criteria section: <ul style="list-style-type: none"> • Clarification of prescriber specialty criterion with the following ‘healthcare provider experienced in injection procedures of the hand and in the treatment of Dupuytren’s contracture’ In the ‘Reauthorization/Continuation of Therapy’ section, clarification to criterion #1 (intent did not change; clarification to align with the ‘Administration/Quantity Limit and Authorization’ section): <ul style="list-style-type: none"> • Reauthorization request is for treatment of a previously treated cord following recurrence: Member currently meets ALL initial coverage criteria AND member has received less than 3 injections total per cord at 4-weeks apart • For treatment of a new cord, submit new request for initial authorization 	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.*