Xiaflex® (Collagenase Clostridium Histolyticum)

Policy Number: IEXD0226.07
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➲ Instructions for Use

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Related Policies
None

Applicable States

This Medical Benefit Drug Policy applies to Individual Exchange benefit plans in all states except for Massachusetts, Nevada, and New York.

Coverage Rationale

Xiaflex is proven and medically necessary for the treatment of:

- **Dupuytren's contracture when all of the following criteria are met:**
  - For **initial therapy**, **all** of the following:
    - Patient has diagnosis of Dupuytren's contracture with a palpable cord; **and**
    - Patient is 18 years of age or older; **and**
    - Xiaflex is prescribed and administered by a healthcare provider experienced in injection procedures of the hand and in the treatment of Dupuytren's contracture; **and**
    - Documented contracture of at least 20 degrees flexion for a metacarpophalangeal (MP) joint contracture or proximal interphalangeal (PIP) joint contracture; **and**
    - Documentation that the flexion deformity results in functional limitations; **and**
    - Patient has not received surgical treatment on the selected primary joint within the last 90 days; **and**
    - If two injections (two vials) are requested, they are for **one** of the following:
      – One cord affecting two joints in the same finger; **or**
      – Two cords affecting two joints in the same hand
      and
    - Xiaflex dosing is in accordance with the U.S. Food and Drug Administration (FDA) approved labeling: 0.58 mg per injection into a palpable cord; **and**
    - The total number of injections does not exceed three injections per cord at approximately four-week intervals; **and**
    - Authorization is for no more than two injections in the same hand
  - For **continuation of therapy**, **all** of the following:
    - Patient has previously received Xiaflex; **and**
    - Documentation of positive clinical response to Xiaflex; **and**
    - Treatment request is for at least **one** of the following:
      – Metacarpophalangeal (MP) or proximal interphalangeal (PIP) contracture remains in affected cord since previous injection and the contracture is > 5 degrees
      – A different MP or PIP contracture will be injected

and
- If two injections (two vials) are requested, use is for **one** of the following:
  - One cord affecting two joints in the same finger; **or**
  - Two cords affecting two joints in the same hand

  and
- Patient has not received surgical treatment (e.g., fasciectomy, fasciotomy) on the selected primary joint within the last 90 days; **and**
- The previous treatment was at least four weeks ago; **and**
- Xiaflex dosing is in accordance with the U.S. Food and Drug Administration (FDA) approved labeling: 0.58 mg per injection into a palpable cord; **and**
- The total number of injections does not exceed three injections per cord at approximately four-week intervals; **and**
- Authorization is for no more than two injections in the same hand

- **Peyronie's disease when all of the following criteria are met:**
  - For **initial therapy**, **all** of the following:
    - Patient has diagnosis of Peyronie's disease with **both** of the following:
      - Palpable plaque; **and**
      - Curvature deformity of greater than or equal to 30 degrees at the start of therapy

      and
    - Patient is 18 years of age or older; **and**
    - Xiaflex is prescribed and administered by a healthcare provider experienced in the treatment of male urological diseases; **and**
    - Xiaflex dosing is in accordance with the U.S. Food and Drug Administration (FDA) approved labeling: 0.58 mg per injection into a Peyronie's plaque; **and**
    - Authorization is for no more than two injections and 6 weeks duration
  - For **continuation of therapy**, **all** of the following:
    - Patient has previously received Xiaflex; **and**
    - Documentation of positive clinical response to Xiaflex; **and**
    - Last treatment was at least six weeks ago; **and**
    - Documented curvature deformity of ≥ 15 degrees remaining since last treatment cycle; **and**
    - Patient has received less than four treatment cycles [i.e., less than eight injections (two injections per cycle)]; **and**
    - Xiaflex dosing is in accordance with the U.S. Food and Drug Administration (FDA) approved labeling: 0.58 mg per injection into a Peyronie's plaque; **and**
    - Authorization is for no more than two injections and 6 weeks duration

Xiaflex is considered unproven and not medically necessary for any other uses.

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

CPT Code	Description
20527	Injection, enzyme (e.g., collagenase), palmar fascial cord (i.e., Dupuytren's contracture)
26341	Manipulation, palmar fascial cord (i.e., Dupuytren's cord), post enzyme injection (e.g., collagenase), single cord

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

Diagnosis Code	Description
M72.0	Palmar fascial fibromatosis [Dupuytren]
N48.6	Induration penis plastica

Background

Dupuytren's contracture is a relatively common disorder characterized by progressive fibrosis of the palmar fascia.[4] It is a benign, slowly progressive fibroproliferative disease of the palmar fascia. Initial fascial thickening is usually seen as a nodule in the palm, which can be painful or painless and often goes unnoticed and undiagnosed. Joint stiffness and a loss of full extension develop insidiously over a variable period of time but typically decades. As the process evolves, nodules may progress over years to form longitudinal bands referred to as cords on the palmar fascia, and the finger gradually loses extension, with contractures that draw one or more fingers into flexion at the metacarpophalangeal (MCP) joint, proximal interphalangeal (PIP) joint, or both. The term Dupuytren disease (DD) is also used for this disorder, as the fingers are not always held in a fixed flexion deformity. The cause of Dupuytren's contracture is unknown; important factors include genetics, ethnicity, sex, and age and may include certain environmental factors and other diseases. The disorder, which most affects those of northern European ancestry, appears to have a pronounced genetic predisposition; 68 percent of male relatives of affected patients develop the disease. In a study involving patients from the Netherlands, Germany, and the United Kingdom, six of nine genetic loci found associated with genetic susceptibility to Dupuytren's disease contained genes encoding proteins in the Wnt-signaling pathway. Overstimulation of this pathway, which can regulate cellular proliferation, could potentially lead to fibroblast proliferation and nodule formation in this disorder through effects upon beta-catenin. Pathologically, Dupuytren's contracture is characterized by fibroblastic proliferation and disorderly collagen deposition with fascial thickening. Formation of a nodule or nodules occurs in the early proliferative stage of the disease and is the pathognomonic lesion of Dupuytren's contracture. Nodules form due to proliferation of fibroblasts in the superficial palmar fascia and histologically are composed of fibroblasts and type III collagen. Smooth muscle fibroblasts and myofibroblasts are present in the nodules; increased concentrations of prostaglandins are also found within the nodules and may influence myofibroblast contractility. The flexor tendons are not intrinsically involved, but invasion of the dermis occurs and results in characteristic puckering and tethering of the skin. The presence of CD3-positive lymphocytes and the expression of major histocompatibility complex (MHC) class II proteins also suggest a possible role for a T-cell mediated autoimmune response in this disorder.[3,4,5]

Peyronie's disease is an acquired penile abnormality caused by fibrosis of the tunica albuginea, which may lead to pain, deformity, erectile dysfunction, and/or distress. It is thought that repeated minor trauma to the penis initiates a cascade involving extravascular protein deposition, fibrin trapping, and overexpression of cytokines, leading to collagen changes characteristic of the condition. Males around 50 years of age are most commonly affected. Peyronie's disease has a variable course; for most patients, pain will resolve over time without intervention, but curvature deformities are less likely to resolve without treatment. Intralesional therapy with Xiaflex may be used to treat curvature associated with Peyronie's disease and is supported by American Urological Association guidelines.[6]

Benefit Considerations

Some Certificates of Coverage allow for coverage of experimental/investigational/unproven treatments for life-threatening illnesses when certain conditions are met. The member specific benefit plan document must be consulted to make coverage decisions for this service. Some states mandate benefit coverage for off-label use of medications for some diagnoses or under some circumstances when certain conditions are met. Where such mandates apply, they supersede language in the benefit document or in the medical or drug policy. Benefit coverage for an otherwise unproven service for the treatment of serious rare diseases may occur when certain conditions are met. Refer to the Policy and Procedure addressing the treatment of serious rare diseases.

Clinical Evidence

Dupuytren's Contracture

The efficacy of 0.58 mg of collagenase clostridium histolyticum was evaluated in two randomized, double-blind, placebo-controlled, multi-centered trials (CORD I and II) in 374 adult patients with Dupuytren's contracture. At study entry, patients must have had: (1) a finger flexion contracture with a palpable cord of at least one finger (other than the thumb) of 20° to 100° in a metacarpophalangeal (MP) joint or 20° to 80° in a proximal interphalangeal (PIP) joint and (2) a positive "table top test" defined as the inability to simultaneously place the affected finger(s) and palm flat against a table top. Patients could not have received a surgical treatment (e.g., fasciectomy, fasciotomy) on the selected primary joint within 90 days before the first injection of study medication and patients could not have received anticoagulation medication (except for up to 150 mg of aspirin per day) within seven days before the first injection of study medication.

The cord affecting the selected primary joint received up to three injections of 0.58 mg of collagenase clostridium histolyticum or placebo on days 0, 30, and 60. About 24 hours after each injection of study medication, if needed, the investigator manipulated (extended) the treated finger in an attempt to facilitate rupture of the cord (finger extension

procedure). Following manipulation, patients were fitted with a splint, instructed to wear the splint at bedtime for up to four months, and instructed to perform a series of finger flexion and extension exercises each day.

In these two studies, the primary endpoint was to evaluate the proportion of patients who achieved a reduction in contracture of the selected primary joint (MP or PIP) to within 0° to 5° of normal, 30 days after the last injection of that joint on days 30, 60, or 90 (after up to three injections). A greater proportion of collagenase clostridium histolyticum-treated patients compared to placebo-treated patients achieved the primary endpoint. The proportion of patients who achieved a contracture reduction of the primary joint to 0° to 5° after the first injection was 39% and 1% in CORD I and 27% and 5% in CORD II in the collagenase clostridium histolyticum and placebo groups respectively. Collagenase clostridium histolyticum-treated patients, compared to placebo-treated patients, showed a greater increase from baseline in the range of motion of MP and PIP joints.

A long term, observational, Year 2 to Year 5 follow-up study was undertaken to evaluate recurrence of contracture and long-term safety in subjects who received up to eight single injections of collagenase clostridium histolyticum 0.58 mg in a previous Phase 3 open-label or double-blind with open-label extension study. Of the 950 patients eligible, only 645 patients enrolled. Of the 645 patients enrolled, 30% discontinued the study. Recurrence was assessed in successfully treated joints (i.e., subjects had a reduction in contracture to 5° or less at the day 30 evaluation after the last injection of collagenase clostridium histolyticum in a previous study) and was defined as an increase in joint contracture by at least 20° in the presence of a palpable cord, or the joint underwent medical or surgical intervention primarily to correct a new or worsening Dupuytren's contracture in that joint. More than 50% of joints successfully treated with collagenase clostridium histolyticum maintained response for five years.

Study 5 retreated a subset of patients from Study 4 for a joint that was previously successfully treated but had recurrence. Patients in Study 5 received up to three injections of collagenase clostridium histolyticum (0.58 mg). Of the 91patients eligible for Study 5, 52 patients enrolled. In Study 5, 65% of recurrent MP joints and 45% of recurrent PIP joints achieved clinical success after retreatment with up to three injections of collagenase clostridium histolyticum. There was no control group for comparison in Study 5.

Peyronie's Disease

The efficacy of collagenase clostridium histolyticum was evaluated in two randomized, double-blind, placebo-controlled, multi-centered trials (IMPRESS I and II) in 832 adult males with Peyronie's disease. At study entry, patients must have had penile curvature deformity of at least 30 degrees in the stable phase of Peyronie's disease. Patients were excluded if they had a ventral curvature deformity, an isolated hourglass deformity or a calcified plaque that could have interfered with the injection technique. At baseline, penile pain was either not present or was mild in most (98%) patients.

In these trials, patients were given up to four treatment cycles of collagenase clostridium histolyticum or placebo (weeks 0, 6, 12, 18), and were followed in a non-treatment follow-up period (weeks 24 -52). In each treatment cycle, two injections of collagenase clostridium histolyticum or two injections of placebo were administered one to three days apart. A penile modeling procedure was performed on patients at the study site one to three days after the second injection of the cycle. The treatment cycle was repeated at approximately six-week intervals for up to three additional times, for a maximum of eight total injection procedures and four total modeling procedures. In addition, patients were instructed to perform penile modeling at home for six weeks after each treatment cycle.

Before the first dose of study drug was administered, eligible subjects were stratified by the degree of curvature deformity (30 to 60 degrees, and 61 to 90 degrees) and then randomized into two treatment groups to receive either collagenase clostridium histolyticum or placebo in a 2:1 ratio. The efficacy population [modified intent-to-treat (mITT) population] comprised a total of 612 intent-to-treat subjects who had both a curvature deformity measurement and a PDQ assessment at baseline, and at one or more subsequent time points in IMPRESS I and II, and had engaged in vaginal intercourse within three months prior to each PDQ assessment.

In IMPRESS I and II, the co-primary endpoints were the percent change from baseline to week 52 in penile curvature deformity and the change from baseline to Week 52 in the Bother domain score of the PDQ. The Bother domain score is a composite of the following patient-reported items: concern about erection pain, erection appearance, and the impact of Peyronie's disease on intercourse and on frequency of intercourse.

Penile curvature deformity (co-primary endpoint) collagenase clostridium histolyticum treatment significantly improved penile curvature deformity in patients with Peyronie's disease compared with placebo. Change from baseline with collagenase clostridium histolyticum treated patients was 33%. The improvement in curvature deformity was numerically similar among subjects with baseline curvature deformity from 30 to 60 degrees and those with curvature deformity from 61 to 90 degrees.

Peyronie's Disease Questionnaire Bother domain score (co-primary endpoint) collagenase clostridium histolyticum significantly reduced patient-reported bother associated with Peyronie's disease compared with placebo. The reduction in the bother domain score was numerically similar between patient groups stratified by degree of baseline curvature deformity (30 to 60 degrees, and 61 to 90 degrees). IMPRESS I had a 37.3% reduction in Bother and IMPRESS II a 35.1% reduction.

A total of eight prospective single-arm studies, plus one retrospective single-arm study have investigated the clinical efficacy of collagenase clostridium histolyticum (CCH) for Peyronie's disease (PD).[7] The treatment protocols exhibited considerable homogeneity between studies in terms of dosage (0.58 mg in all studies) and injection programs, which ranged from three to four cycles of two injections with an interval of 24–72 h between each injection. Only one study evaluated the effect of CCH therapy combined with a vacuum device. Improvements in penile curvature (PC) ranged from -22.6 to -12.7 in studies reporting significant absolute changes, and -36.3% in the one study that reported a percentage decrease. Raheem and colleagues evaluated the effects of CCH therapy combined with vacuum pump device, and reported clinically and statistically meaningful improvements in PC compared with baseline (from 54.17 to 37).[8] By contrast, Nguyen et al. did not report any significant benefit of CCH injections, in patients with either early (60.0 vs 43.9) or chronic (56.9 vs 41.3) PD between baseline and the final follow-up point.[9] Similarly, Anaissie and colleagues did not demonstrate significant changes in PC after CCH injections.[10] Considering secondary outcomes, only Jordan reported a significant reduction in plaque length (-0.941 inches) and width (-0.0129 inches), whereas Raheem et al. reported an increase in International Index of Erectile Function (IIEF-5) compared with baseline (23.75 vs 20.90).[8,11] The magnitude of improvement in penile pain (PP) reported across studies, evaluated with the use of the Peyronie's Disease Questionnaire—penile pain domain, ranged from -5.3 to -2.4, and a reduction of -1.64 was described when CCH therapy was combined with a vacuum device. For penile length (PL), only the study by Levine et al. reported significant changes between baseline and final follow-up (10.6 vs 11.0 cm).[12] The other three studies that reported PL did not demonstrate a significant benefit of CCH on this parameter. A study by Cocci et al. found that IIEF, PC, PS, PP, and PL significantly improved after treatment and observed a mean change of 19.1 of PC after treatment (three intralesional injections of 0.9 mg performed at 4-wk intervals).[13]

U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

Xiaflex is a combination of bacterial collagenases indicated for the treatment of adult patients with Dupuytren's contracture with a palpable cord and the treatment of adult men with Peyronie's disease with a palpable plaque and curvature deformity of at least 30 degrees at the start of therapy.

Because of the risks of corporal rupture (penile fracture) or other serious penile injury in the treatment of Peyronie's disease, Xiaflex is available only through the Xiaflex Risk Evaluation and Mitigation Strategy (REMS) Program.

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 Peyronie's disease.
- Healthcare sites must be certified with the program and ensure that Xiaflex is only dispensed for use by certified prescribers.

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Policy History/Revision Information

Date	Summary of Changes
01/01/2026	**Supporting Information** • Added *Benefit Considerations* section • Archived previous policy version IEXD0226.06

Instructions for Use

This Medical Benefit Drug Policy provides assistance in interpreting UnitedHealthcare benefit plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plan may differ from the standard benefit plan. In the event of a conflict, the member specific benefit plan document governs. Before using this policy, check the member specific benefit plan document and any applicable federal or state mandates. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Medical Benefit Drug Policy is provided for informational purposes. It does not constitute medical advice.

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