Health Partners Plans HPP

DR.010.B Xiaflex™ (Collagenase clostridium histolyticum)

Original Implementation Date : 08/1/2021
Version [B] Date : 10/1/2022
Last Reviewed Date: 9/21/2022

PRODUCT VARIATIONS

This policy applies to all Health Partners Plans (HPP) product lines unless noted below.

POLICY STATEMENT

Health Partners Plans (HPP) considers Xiaflex™ (Collagenase clostridium histolyticum) medically necessary for its FDA approved indications when the prior authorization criteria listed in this policy are met.

OFF-LABEL USE

Authorization for off-labeled use of medication will be evaluated on an individual basis. Review of an off-labeled request by the Medical Staff will be predicated on the appropriateness of treatment and full consideration of medical necessity. For off-label use Medical Directors will review scientific literature and local practice patterns.

FDA APPROVED INDICATIONS

Xiaflex™ is a combination of bacterial collaganases indicated for the treatment of:

- Adult (≥18-years-old) patients with Dupuytren's contracture with palpable cord.
- Adult (≥18-years-old) men with Peyronie's disease with a palpable plaque and curvature deformity of at least 30 degrees and less than 90 degrees at the start of therapy.

PRIOR AUTHORIZATION CRITERIA

INITIAL CRITERIA

1) Is the patient at least 18 years of age or older? *If YES, go to 8. If NO, refer to Medical Director.*

2) Does the patient have documentation of a diagnosis of Dupuytren's contracture with palpable cord? *If YES, go to 3. If NO, go to 7.*

3) Does the patient have functional impairment with both:
   a. Positive "table-top" test (inability to simultaneously place affected finger and palm flat on a flat surface).
   b. Metcarpophalangeal (MCP) contracture of at least 20 degrees or proximal interphalangeal (PIP) contracture of at least 20 degrees.

   If yes, go to 4. If no, refer to Medical Director.

4) Is the medication prescribed by or in consultation with a physician who is a hand specialist or experienced in injection procedures of the hand? *If YES, go to 5. If NO, refer to Medical Director.*

5) Will the patient receive comprehensive treatment based on standards of care for Dupuytren's contracture (e.g., finger extension after injection)? *If YES, go to 6. If NO, refer to Medical Director.*

6) Is the prescribed medication Xiaflex™ requested for a maximum of 2 injections per hand (0.58 mg per injection site), for a maximum of 3 treatment cycles 4 weeks apart. *If yes, approve for 3 months. If no, contact the Medical Director.*

7) Is the patient a male who has documentation of a diagnosis of Peyronie's Disease with at curvature of >30 degrees and palpable plaque? *If YES, go to 8. If NO, refer to Medical Director.*

8) Does the patient have any contraindications to the requested drug for the treatment of Peyronie's disease, such as a history of hypersensitivity to Xiaflex™ or to collagenase used in other therapeutic applications, or have Peyronie's plaque that involves the penile urethra? *If NO, go to 9. If YES, refer to Medical Director.*

9) Does the member have intact erectile function (with or without medication*)?* If YES, go to 10. If NO, refer to *Medical Director.*

10) Is the medication prescribed by or in consultation with a urologist or physician who is experienced in the treatment of male urological diseases? *If YES, go to 11. If NO, refer to Medical Director.*

11) Will the patient receive comprehensive treatment based on standards of care for Peyronie's Disease (i.e., penile modeling activities after injection)? *If YES, go to 12. If NO, refer to Medical Director.*

12) Is the prescriber and healthcare site certified with the Xiaflex™ REMS program if prescribing for the treatment of Peyronie's disease? *If YES, go to 13. If NO, refer to Medical Director.*

13) Is the prescribed medication Xiaflex™ requested for a maximum of 4 treatment cycles at 6 weeks intervals (each cycle of 2 0.58 mg injections into the target plaque separated by 1 to 3 days)?" I*f YES, approve for 5 months. If NO, refer to Medical Director.*

RENEWAL CRITERIA

1) Does the patient continue to meet the diagnostic criteria after initial treatment of Xiaflex™ for Dupuytren's contracture with palpable cord (and contracted cord persists) or Peyronie's Disease with palpable plaque and curvature of >15 degrees? *If YES, go to 2. If NO, refer to Medical Director.*

2) Does the patient have the absences of unacceptable toxicity which precludes safe administration of the drug? (Examples of unacceptable toxicity include the following: corporal or tendon rupture, severe penial hematoma, hypersensitivity reactions, etc.) *If YES, go to 3. If NO, refer to Medical Director.*

3) Will the patient continue to receive comprehensive treatment based on standards of care for Dupuytren's contracture or Peyronie's Disease (examples include the following: finger extension or penile modeling procedures after injection)? *If YES, go to 4. If NO, refer to Medical Director.*

4) Is the patient receiving clinical benefit based on the prescriber's assessment? *If YES, approve for 1 month. If NO, refer to Medical Director.*

NOTE: Maximum of 3 treatment cycles for Dupuytren's contracture per cord (unless contracted cord persists) and maximum of 4 treatment cycles for each plaque for Peyronie's Disease.

DOSAGE AND ADMINISTRATION

Single-use glass vials containing 0.9 mg of collagenase clostridium histolyticum as a sterile, lyophilized powder for reconstitution. Sterile diluent for reconstitution is also provided in a single-use glass vial.

Dosing recommendations for Duputren's contracture:

- Inject 0.58mg of Xiaflex™ into each palpable Dupuytren cord with a contracture of the metacarpophalangeal (MP) joint or a proximal interphalangeal (PIP) joint according to the injection procedure.
- Up to 2 joints in the same hand may be treated during the visit.
- Approximately 24 to 72 hours following injection, perform a finger extension procedure if a contracture persists.
- Injections and finger extension procedures may be administered up to 3 times per cord at approximately 4-week intervals.
- Inject up to two cords in the same hand at a treatment visit. If a patient has other cords with contractures, inject those cords at another treatment visit.

Dosing recommendation for Pyeronie's Disease:

- A treatment cycle consists for two Xiaflex™ injection procedures and a penile modeling procedure.
- Induce a penile erection. A single intracavernosal injection of 10 or 20 micrograms of alprostadil may be used to induce penile erection to mark the target area in the Peyronie's plaque.
- With the penis in the erect state, identify and mark the target area in the Peyronie's plaque to be injected.
- Penis must be flaccid before injecting Xiaflex™.
- Inject 0.58 mg Xiaflex™ into the target plaque once on each of two days, 1 to 3 days apart, according to the injection procedure.
- Perform penile modeling activities 1 to 3 days after the second injection of each treatment cycle.
- For each plaque causing the curvature deformity, repeat every 6 weeks for up to 4 treatment cycles may be administered.
- If the curvature deformity is less than 15 degrees after the first, second or third treatment cycle, or if further treatment is not clinically indicated, then subsequent treatment cycles should not be administered.

RISK FACTORS/SIDE EFFECTS

- **Hypersensitivity reactions, including anaphylaxis**: Healthcare providers should be prepared to address hypersensitivity reactions, including anaphylaxis, following Xiaflex™ injections.

- **Patients with abnormal coagulation:** Use with caution, including in patients who have received anticoagulant medications other than low-dose aspirin (<150mg/day) within 7 days of the injection due to the enhancement of injection site bruising and/or bleeding may be increased. If used together, monitor patient closely for signs and symptoms of excessive bruising and/or bleeding. In addition, it is recommended to avoid use of Xiaflex™ in patients with coagulation disorders, including patients receiving concomitant anticoagulants (except for low-dose aspirin).

- **Increased chance of bleeding:** Bleeding or bruising at the injection site can happen in people who receive Xiaflex™**.**

- **Dupuytren's contracture:** The most common adverse reactions reported in ≥ 25% of patients treated with Xiaflex™ and at an incidence greater than placebo were peripheral edema (e.g., swelling of the injected hand), contusion, injection site hemorrhage, injection site reaction, and pain in the injected extremity.

- **Tendon rupture or serious injury to the injected finger/hand:** Avoid injecting Xiaflex™ into tendons, nerves, blood vessels, or other collagen-containing structure of the hand. Injection into these structures may result in possible permanent injury, such as tendon rupture, ligament damage, or skin laceration.

- **Nerve injury or other serious injury of the hand:** if you get numbness, tingling, increased pain, or tears in the skin (laceration) in your treated finger or hand after your injection or after your follow-up visit.

- **Peyronie's Disease:** The most frequently reported adverse drug reactions reported with ≥ 25% of patients treated with Xiaflex™ and at an incidence greater than placebo were penile hematoma, penile swelling, and penile pain.

- **Corporal rupture (penile fracture) or other serious injury to the penis:** Avoid injecting into the urethra, nerves, blood vessels, corpora cavernosa or other collagen-containing structures of the penis. Injection into these structures may result in possible permanent injury such as corporal rupture (penile fracture).

MONITORING

Efficacy

- Physical Findings
  - Dupuytren's contracture
    - Improvement in range of motion in affected hand(s)
  - Peyronie disease
    - Improvement in curvature deformity
    - Decreased pain during erection

Safety

- Side effects seen with Xiaflex™ are localized to the site of injection. Look for sign and symptoms stated above in Risk Factors/Side Effects section to ensure safety.

BLACK BOX WARNING

CORPORAL RUPTURE (PENILE FRACTURE) OR OTHER SERIOUS PENILE INJURY IN THE TREATMENT OF PEYRONIE'S DISEASE:

Corporal rupture (penile fracture) was reported as an adverse reaction in 5 of 1044 (0.5%) Xiaflex™-treated patients in clinical studies. In other Xiaflex™-treated patients (9 of 1044; 0.9%), a combination of penile ecchymoses or hematoma, sudden penile detumescence, and/or a penile "popping" sound or sensation was reported, and in these cases, a diagnosis of corporal rupture cannot be excluded. Severe penile hematoma was also reported as an adverse reaction in 39 of 1044 (3.7%) Xiaflex™-treated patients. Signs or symptoms that may reflect serious penile injury should be promptly evaluated to assess for corporal rupture or severe penile hematoma which may require surgical intervention.

Because of the risks of corporal rupture or other serious penile injury, Xiaflex™ is available for the treatment of Peyronie's disease only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the Xiaflex™ REMS Program.

CLINICAL EVIDENCE

DUPUYTREN'S CONTRACTURE

The efficacy of 0.58 mg of Xiaflex was evaluated in two randomized, double-blind, placebo controlled, multi-centered trials in 374 adult patients with Dupuytren's contracture (Studies 1 and 2). 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 "tabletop test" defined as the inability to simultaneously place the affected finger(s) and palm flat against a tabletop. 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 7 days before the first injection of study medication.

The cord affecting the selected primary joint received up to 3 injections of 0.58 mg of Xiaflex™ 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 4 months, and instructed to perform a series of finger flexion and extension exercises each day.

RESULTS: In Studies 1 and 2, 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 3 injections). The results demonstrate a greater proportion of Xiaflex™-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 Study 1 and 27% and 5% in Study 2 in the Xiaflex™ and placebo groups respectively. Xiaflex™-treated patients, compared to placebo-treated patients, showed a greater increase from baseline in the range of motion of MP and PIP joints.

PEYRONIE'S DISEASE

The efficacy of Xiaflex™ was evaluated in two randomized, double-blind, placebo-controlled, multi-centered trials in 832 adult males with Peyronie's disease (Studies 1 and 2). 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 4 treatment cycles of Xiaflex™ 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 Xiaflex ™ or two injections of placebo were administered 1 to 3 days apart. A penile modeling procedure was performed on patients at the study site 1 to 3 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 8 total injection procedures and 4 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 Xiaflex ™ 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 Studies 1 and 2 and had engaged in vaginal intercourse within 3 months prior to each PDQ assessment.

In Studies 1 and 2, 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.

RESULTS: Xiaflex™ treatment significantly improved penile curvature deformity in patients with Peyronie's disease compared with placebo. 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. Xiaflex™ 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). There were no clinically meaningful differences in the mean percent improvement in curvature deformity or mean reduction in the bother domain score following treatment with Xiaflex based on the severity of baseline erectile dysfunction or concomitant phosphodiesterase type 5 (PDE5) inhibitor use.

BACKGROUND

DUPUYTREN'S CONTRACTURE

Dupuytren disease is predominantly a benign, slowly progressive myofibroblastic disease that affects the palmar and digital fascia of the hand that can lead to contracture deformities. The most commonly affected fingers are the fourth (ring) and fifth (small or pinky) digits. 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. Myofibroblast have contractile actin microfilaments that aligns with the long axis of the cell and interconnects themselves with fibronectin and excellular fibril. Type III collagen buildup and predominates the extracellular matrix; about 10% of the cells in Dupuytren's nodules are comprised of immune cells with majority of them being macrophages and lymphocytes. Macrophages and lymphocytes are responsible for the secretion of proinflammatory cytokines including interleukin-6 (IL-6), IL-8, and tumor necrosis factor (TNF) which may influence myofibroblast contractility. Nodules are densely packed with T-cell infiltrates, suggesting a T-cell mediated autoimmune disorder. In-vitro studies have shown cells expressing restricted T-cell receptors. This can help support the concept that a local immune reaction triggered by autoantigen may be caused by microvascular changes in the hand.

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. The transformation of normal fascial bands is what causes the contracture of the hand. Central cords originate from the pre-tendinous bands and can cause pitting edema in the hand and MCP joint contracture. Natatory cords are responsible for webspace contractures. Spiral cords are most important as the disease process and can cause PIP contracture. Joint stiffness and loss of full extension develops typically over decades but can vary depending on patient demographics and risk factors.

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. Dupuytren contracture is most commonly found in patients with Northern European/Scandinavian descent. It is uncommon in patients who are South European and South American populations and rarely seen in patients who are African and Asian. In Asian populations, the palm is more likely to be involved than the digits and often goes unnoticed. Males are more at risk at being diagnosed with Dupuytren's contracture than women in a 2:1 ratio and are more likely to be at risk for severe disease.

Risk factors for increased severity and recurrence of disease after treatment include:

1) Male gender.
2) Onset before age 50.
3) Bilateral disease.

4) Sibling/parent involvement.
5) Presence of Garrod pads, Ledderhose, or Peyronie's diseases.

Dupuytren's contracture has also been observed in association with the following conditions and habits:

- Cigarette Smoke/Alcohol consumption.
- Diabetes Mellitus.
- Palmar fasciitis.
- Workers exposed to repetitive handling tasks or vibration as compared with those not exposed such trauma, although this association remains controversial.

There are also genetic factors involved in Dupuytren 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.

The disease is not always progress and about 50-70% of patients may stabilize or regress. There is still some information that remains to be discovered with the molecular signaling pathway as disease progresses and how we can create more treatment targets for this disease.

PEYRONIE'S DISEASE

Peyronie's disease is a penile abnormality characterized by the fibrosis of tunica albuginea that may cause pain, deformity, erectile dysfunction, and/or distress. It is an acquired inflammatory disorder that causes microvascular trauma to the penile shaft; this can cause penis to buckle in the erect or semi-erect state. This repetitive minor trauma to the penis imitates a cascade involving significant extravascular protein deposition, fibrin trapping, macrophage recruitment, cytokine overexpression, and release of elastase that leads to the changes of the tunical collagen from type 1 to predominantly type 3 collagen. The trauma is also associated with changes in the tunica's elastin leading to scarring and inelasticity. The natural degradation of fibrin may be altered secondarily to proteins, such as transforming growth factor 1 and plasminogen activator inhibitor type 1, leading to irregular tunical healing. Plaque can restrict tunical lengthening on the affected side during erection, which can lead to penile curvature, ED, and/or penile deformity, discomfort, and pain.

Peyronie's disease is thought to be due to localized aberration of the wound healing process. For susceptible individuals, bleeding within the tunica albuginea, trapping of fibrin and inflammatory cells, and overexpression of matrix proteins secondary to upregulation of cytokines and growth factors in the local environment lead to plaque formation. Excess fibrin deposition in response to microvascular injury and upregulation of transforming growth factor (TGF)-1 results in one or more areas of plaque formation.

American Urology Association maintains the diagnosis and treatment guidelines for Peyronie's disease. Peyronie's Disease is known to have two types of disease states, which are active and

stable; it is useful to identify if the patient has active or stable disease because it can help determine the type of treatment the patient receives benefit based on if the symptoms are dynamic or stable.

Active Disease: It is characterized by dynamic and changing symptoms. The defining symptoms of the active stage can be penile and/or glandular pain and discomfort with or without erection. Symptom onset may be associated with penile buckling during intercourse. The patient may not manifest the penile induration, or a palpable plaque associated with painful penile deformity and curvature. Plaque(s) and penile deformities, including curvature (dorsal, lateral, ventral), shortening, indentation, hinge effect, narrowing, or hourglass deformity, may not be fully developed at this stage. Distress may be present in response to pain and to progressive deformity. Erectile function may be intact or may be compromised by pain and/or developing deformity.

Stable Disease: In stable disease, symptoms have been clinically quiescent or unchanged for at least three months based on patient reports or clinical documentation. Pain with or without erection may be present but less common. In stable disease, the deformity is no longer progressing. Curvature may be uniplanar or biplanar and may not be dependent on plaque size and magnitude. Plaque can be palpated or documented on ultrasound. The most common location of the plaque is on the mid shaft dorsal aspect of the penis toward the penile hilum or distally retrocoronal. The typical patient presents with a dorsal, dorso-lateral, or ventral penile deformity. Rarely rotational deformities may occur. There may be additional manifestations in the stable phase, including difficulty in maintaining erectile function and inability to sustain intercourse. Erectile function may be compromised by pain and/or deformity or may be reduced because of symptoms of ED not related to deformity or pain. It is reported that ED may be present in up to 33% of PD patients with greater than 50% of patients reporting that ED predated the onset of PD symptoms. Distress is generally present, and the degree of distress will depend on the patient's perception of his symptom severity.

Peyronie's disease symptoms can be characterized as variable as some may improve or resolve without treatment in some patients. Data suggest that for many or most patients pain will resolve over time without intervention. Curvature and other types of deformities are much less likely to improve and may require treatment if it compromises sexual function and/or is the source of patient or partner distress. Additionally, the stress of Peyronie's Disease often extends to the men's relationships; more than half (54%) report that some of their Peyronie's Disease negatively affects their relationships. Men have also expressed concerns about decrease in sexual satisfaction and how the physical appearance of their penis affects how they perceive their masculinity. They also report increased anxiety in a sexual situation, a decrease in sexual confidence, and a concern that they are not satisfying their partner. Lastly, men with PD report a sense of isolation as they find it difficult to communicate with their healthcare professionals or partners about Peyronie's Disease. With these issues in mind, the American Urology Association stresses the importance of assessing for distress in the PD patient before treatment begins and during treatment course.

CODING

Note*:* The Current Procedural Terminology (CPT®), Healthcare Common Procedure Coding System (HCPCS), and the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) codes that *may* be listed in this policy are for reference purposes only. Listing of a code in this policy does not imply that the service is covered and is not a guarantee of payment. Other policies and coverage guidelines may apply. When reporting services,

providers/facilities should code to the highest level of specificity using the code that was in effect on the date the service was rendered. This list may not be all inclusive.

CPT® is a registered trademark of the American Medical Association.

CPT Code	Description
20527	Injection, enzyme (e.g., collagenase), palmar fascial cord (i.e., Dupuytren's contracture)
20550	Injection(s); single tendon sheath, or ligament, aponeurosis (e.g., plantar "fascia")
26341	Manipulation, palmar fascial cord (i.e., Dupuytren's cord), post enzyme injection (e.g., collagenase), single cord
54200	Injection procedure for Peyronie disease;
54205	Injection procedure for Peyronie disease; with surgical exposure of plaque

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

ICD-10 Codes	Description
N48.6	Induration penis plastica
M72.0	Palmar fascial fibromatosis [Dupuytren]

DISCLAIMER

Approval or denial of payment does not constitute medical advice and is neither intended to guide nor influence medical decision making.

Policy Bulletins are developed by Health Partners Plans (HPP) to assist in administering plan benefits and constitute neither offers of coverage nor medical advice.

This Policy Bulletin may be updated and therefore is subject to change.

For HealthChoices (Medicaid) and Children's Health Insurance Program (CHIP) products: Any requests for services that do not meet criteria set in PARP will be evaluated on a case-by-case basis.

POLICY HISTORY

This section provides a high-level summary of changes to the policy since the previous version.

Summary	Version	Version Date
2022 Annual Review. The following sections of the policy were updated: Prior Authorization Criteria, Dosing and Administration, Risk Factors. A new section was added for Clinical Trials. Policy version changed from "A" to "B".	B	10/01/2022
New policy.	A	08/01/2021

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