Xiaflex AHM

Clinical Indications

- **Xiaflex**
  - Xiaflex (Collagenase clostridium histolyticum) injections are considered medically necessary **1 or more** of the following
    - Treatment of adults with Dupuytren's contracture with a palpable cord.
    - Xiaflex (collagenase Clostridium histolyticum) for the treatment of Peyronie's disease is considered medically necessary when it is administered under the Risk Evaluation and Mitigation Strategy (REMS) program. (Note: A treatment course for Peyronie's disease consists of a maximum of 4 treatment cycles (each separated by 6 weeks). Each treatment cycle consists of 2 Xiaflex injection procedures (in which Xiaflex is injected directly into the collagen-containing structure of the penis) and 1 penile modeling procedure).
- Dosage and Monitoring: Injections of Xiaflex may be administered up to 3 times per cord at approximately 4-week intervals. Only 1 cord should be injected at a time. If patients have other cords with contractures of MCP or PIP joints, these cords should be injected in sequential order.

Evidence Summary

Background

- Dupuytren's disease, a progressive fibro-proliferative disorder, is characterized by nodule formation and contracture of the palmar fascia, and may result in flexion deformity of the fingers and loss of hand function. The disease is common in men older than 40 years; in persons of Northern European descent; and in persons who smoke, use alcohol, or have diabetes mellitus. The symptoms of Dupuytren's contracture are often mild and painless and do not require treatment. Patients present with a small, pitted nodule (or multiple nodules) on the palm, and may stay the same for months or years. In some patients, however, it may progress to the next stage, in which cords of fibrous tissue form in the palm and run into the fingers or thumb, eventually, pulling them into a permanently flexed position, making it difficult to perform activities of daily living

- The disease initially can be managed with observation and non-surgical therapy. It will regress without treatment in about 10% of patients. Injection of steroids into the nodule has been shown to reduce the need for surgery. Surgical referral should be made when metacarpophalangeal (MCP) joint contracture reaches 30 degrees or when proximal interphalangeal (PIP) joint contracture occurs at any degree. In-office percutaneous needle aponeurotomy is an alternative to surgery (Trojian and Chu, 2007).
- Swartz and Lalonde (2008) stated that treatment of Dupuytren's disease is offered to symptomatic patients with painful nodular or disabling contracture. Limited fasciectomy of the involved abnormal structures followed by hand therapy is standard treatment, but it is associated with serious potential complications. Moreover, recurrence is common. New treatments include the injection of clostridial collagenase, which works by breaking down the excessive build-up of collagen in the hand.
- In a phase II open-label clinical trial, Badalamente and Hurst (2000) examined the clinical safety and effectiveness of clostridial collagenase injection as a non-surgical treatment of Dupuytren's disease. A total of 35 patients entered the study (3 women and 32 men). The mean age was 65 years. The first 6 patients were treated following a dose escalation protocol and received 300, 600, 1200, 2400, 4800, and 9600 units (U) collagenase injected into the cord that was causing contracture of the MCP joint. There were no beneficial clinical effects of these injections. The remaining 29 patients had collagenase injections at a dose level of 10,000 U into cords that are causing contractures of 34 MCP joints, 9 PIP joints, and 1 thumb. Twenty-eight of the 34 MCP joint contractures corrected to normal extension (0 degrees) and 2 of the 34 MCP joint contractures corrected to 5 degrees of normal extension, with full range of motion, within 1 to 14 days of injection. In patients with PIP joint contractures, 4 of the 9 joints corrected to normal (0 degrees). One PIP joint corrected to within 10 degrees of normal and 2 corrected to within 15 degrees of normal. There were 2 failures; these patients required surgery. The mean follow-up period was 20.0 +/- 5.6 months for the MCP joints and 14.1 +/- 6.6 months for the PIP joints. Clostridial collagenase injection of Dupuytren's cords causing MCP and PIP joint contractures appears to have merit as non-surgical treatment of this disorder. The authors stated that pending further placebo, double-blind studies, collagenase injection to treat Dupuytren's disease may be a safe and effective alternative to surgical fasciectomy.
- Badalamente et al (2002) reported that in a series of controlled phase II clinical trials, excessive collagen deposition in Dupuytren's disease has been targeted by a unique non-operative method using clostridial collagenase injection therapy to lyse and rupture finger cords causing MCP and/or PIP joint contractures. A total of 49 patients were treated in a random, placebo-controlled trial of one dose of collagenase versus placebo at 1 center. Subsequently 80 patients were treated in a random, placebo-controlled, dose-response study of collagenase at 2 test centers. The results of these studies indicated that non-

operative collagenase injection therapy for Dupuytren's disease is both a safe and effective method of treating this disorder in the majority of patients as an alternative to surgical fasciectomy.

- In a prospective, randomized, double-blind, placebo-controlled, multi-center study, Hurst et al (2009) examined the effects of injectable collagenase clostridium histolyticum for the treatment of Dupuytren's contracture. These investigators enrolled 308 patients with joint contractures of 20 degrees or more . The primary MCP or PIP joints of these patients were randomly assigned to receive up to 3 injections of collagenase clostridium histolyticum (at a dose of 0.58 mg per injection) or placebo in the contracted collagen cord at 30-day intervals. One day after injection, the joints were manipulated. The primary end point was a reduction in contracture to 0 to 5 degrees of full extension 30 days after the last injection. Twenty-six secondary end points were evaluated, and data on adverse events were collected. Collagenase treatment significantly improved outcomes. More cords that were injected with collagenase than cords injected with placebo met the primary end point (64.0 % versus 6.8 %, $p < 0.001$), as well as all secondary end points ($p <$ or $= 0.002$). Overall, the range of motion in the joints was significantly improved after injection with collagenase as compared with placebo (from 43.9 to 80.7 degrees versus from 45.3 to 49.5 degrees, $p < 0.001$). The most commonly reported adverse events were localized swelling, pain, bruising, pruritus, and transient regional lymph-node enlargement and tenderness. Three treatment-related serious adverse events were reported: 2 tendon ruptures and 1 case of complex regional pain syndrome. No significant changes in flexion or grip strength, no systemic allergic reactions, and no nerve injuries were observed. The authors concluded that collagenase clostridium histolyticum injection significantly reduced contractures and improved the range of motion in joints affected by advanced Dupuytren's disease.
- On February 2, 2010, the Food and Drug Administration approved collagenase clostridium histolyticum (Xiaflex) as the first drug to treat Dupuytren's contracture. Xiaflex is injected directly into the collagen cord of the hand and should be administered only by a health care professional experienced with injections of the hand, because tendon ruptures may occur. The product insert of Xiaflex states that injections may be administered up to 3 times per cord at approximately 4-week intervals. Only 1 cord should be injected at a time. If patients have other cords with contractures of MCP or PIP joints, these cords should be injected in sequential order.
- The most common adverse reactions in patients treated with Xiaflex were peripheral edema (mostly swelling of the injected hand), contusion, injection site reaction, injection site hemorrhage, and pain in the treated extremity. Serious adverse reactions included tendon ruptures and other serious injuries to the injected extremity.
- Clostridial collagenase has also been used in the treatment of Peyronie's disease. Jordan (2008) evaluated the safety and effectiveness of intra-lesional clostridial collagenase

injection therapy in a series of patients with Peyronie's disease. A total of 25 patients (aged 21 to 75 years) who were referred to a single institution with a well-defined Peyronie's disease plaque were treated with 3 intra-lesional injections of clostridial collagenase 10,000 U in a small volume (0.25 cm(3) per injection) administered over 7 to 10 days, with a repeat treatment (i.e., 3 injections of collagenase 10,000 U/25 cm(3) injection over 7 to 10 days) at 3 months. Primary efficacy measures were changes from baseline in the deviation angle and plaque size. Secondary efficacy end points were patient responses to a Peyronie's disease questionnaire and improvement according to the investigators' global evaluation of change. Significant decreases from baseline were achieved in the mean deviation angle at 3 months ($p = 0.0001$) and 6 months ($p = 0.0012$), plaque width at 3 months ($p = 0.0052$), 6 months ($p = 0.0239$), and 9 months ($p = 0.0484$), and plaque length at 3 months ($p = 0.0018$) and 6 months ($p = 0.0483$). More than 50 % of patients in this series considered themselves "very much improved" or "much improved" at all time points in the study, and the drug was generally well-tolerated. The authors concluded that the benefits of intra-lesional clostridial collagenase injections in this trial lend support to prior studies supporting its use in the management of Peyronie's disease. They noted that a double-blind, placebo-controlled study is currently under development.

- Seegenschmiedt et al (2001) presented the 1-year results of a prospective randomized trial that compared two different RT dose concepts for early-stage DC. A total of 129 patients (62 females; 67 males) were entered in this study: 69 had bilateral and 60 unilateral involvement of DC accounting for 198 irradiated hands. According to Tubiana's classification, 73 hands had Stage N (nodules/cords, no extension deficit = flexion deformity), 61 had Stage N/I (less than or equal to 10 degrees deficit), 59 had Stage I (11 to 45 degrees deficit), and 5 had Stage II (46 to 90 degrees deficit) DC. Prophylactic RT was randomly delivered; in Group A, 63 patients (95 hands) received 10 x 3 Gy (total dose of 30 Gy) in 2 series (5 x 3 Gy) separated by 8 weeks; in Group B, 66 patients (103 hands) received 7 x 3 Gy (total dose of 21 Gy) in 1 series within 2 weeks. Ortho-voltage RT (120 kV) was applied using standard cones and individual shielding of un-involved areas of the palm.
- Relevant patient and disease parameters were equally distributed in both groups. Evaluation (toxicity, efficacy) was performed at 3 and 12 months after RT. Subjective (patient's opinion) and objective parameters (measurements, palpation, and comparative photographs) were applied to assess treatment response. Minimum follow-up was 1 year. Acute toxicity was minimal, but slightly more pronounced in Group B. Seventy-six (38 %) hands developed skin reactions common toxicity criteria [CTC] 1 degrees (A, 30; B, 46); and 12 (6 %) had skin reactions CTC 2 degrees (A, 4; B, 8). Chronic side effects were limited to dryness, desquamation, skin atrophy, and change of sensation (LENT 1 degrees) in 9 (5 %) sites without differences between the two groups.

- At 3 and 12 months after RT, subjective and objective reduction of symptoms, nodules, and cords occurred in both groups ($p < 0.01$) with no differences between the groups: in Group A, 55 (56 %) sites regressed, 35 (37 %) remained stable, and 7 (7 %) progressed, whereas in Group B, 55 (53 %) regressed, 39 (38 %) remained stable, and 9 (9 %) progressed at 12-month follow-yp (non-significant). Overall and mean number of nodules, cords, and skin changes decreased at 3 and 12 months. The "treatment failure" rate at 1 year was 16 of 198 (8 %), but only 4 (2 %) sites required hand surgery for disease progression. Seven of 60 patients with unilateral DC received prophylactic RT for the initially un-involved, contralateral hand due to progression of DC.
- The authors concluded that both prophylactic RT concepts have been well-accepted and well-tolerated by patients. Within the first year, they were equally effective to prevent further disease progression of DC and obtain considerable symptomatic improvement. Although 1-year results suggested similar response rates for both treatment groups, long-term follow-up of greater than 5 years has to be awaited for final assessment and recommendation of an optimized RT treatment schedule.
- In a retrospective cohort study, Atroshi et al (2014) compared CCH injections and FSC for DC regarding actual total direct treatment costs and short-term outcomes. Patients aged 65 years or older with previously untreated DC of 30degree or greater in the MCP and/or PIP joints of the small, ring or middle finger were included in this study. The CCH group comprised 16 consecutive patients treated during the first 6 months following the introduction of CCH as treatment for DC at the study center. The controls were 16 patients randomly selected among those operated on with FSC at the same center during the preceding 3 years. Treatment with CCH was given during 2 standard outpatient clinic visits (injection of 0.9 mg, distributed at multiple sites in a palpable cord, and next-day finger extension under local anesthesia) followed by night-time splinting.
- Fasciectomy was carried out in the operating room (day surgery) under general or regional anesthesia using standard technique, followed by therapy and splinting. Outcome measures included actual total direct costs (salaries of all medical personnel involved in care, medications, materials and other relevant costs), and total MCP and PIP extension deficit (degrees) measured by hand therapists at 6 to 12 weeks after the treatment. Collagenase injection required fewer hospital outpatient visits to a therapist and nurse than FSC. Total treatment cost for CCH injection was US$1,418.04 and for FSC US$2,102.56. The post-treatment median (IQR) total extension deficit was 10 (0 to 30) for the CCH group and 10 (0 to 34) for the FSC group. The authors concluded that treatment of DC with 1 CCH injection cost 33 % less than FSC with equivalent effectiveness at 6 weeks regarding reduction in contracture.
- Peimer et al (2013) evaluated long-term safety and effectiveness of CCH after the 3rd year of a 5-year non-treatment follow-up study (Collagenase Option for Reduction of Dupuytren Long-Term Evaluation of Safety Study [CORDLESS study]). This study

enrolled DC patients from 5 previous clinical studies. Beginning 2 years after the 1st CCH injection, these investigators re-evaluated patients annually for joint contracture and safety. Recurrence in a previously successfully treated joint (success = 0degree to 5degree contracture after CCH administration) was defined as 20degree or greater worsening in contracture in the presence of a palpable cord or medical/surgical intervention to correct new or worsening contracture. We assessed partially corrected joints (joints reduced 20degree or more from baseline contracture but not to 0degree to 5degree) for nondurable response, also defined as 20degree or greater worsening of contracture or medical/surgical intervention.

- Of 1,080 CCH-treated joints (648 MCP; 432 PIP; n = 643 patients), 623 (451 MCP, 172 PIP) had achieved 0degree to 5degree contracture in the original study. Of these joints, 35 % (217 of 623) recurred (MCP 27 %; PIP 56 %). Of these recurrences, an intervention was performed in 7 %. Of the 1,080 CCH-treated joints, 301 were partially corrected in the original study. Of these, 50 % (150 of 301; MCP: 38 % [57 of 152]; PIP: 62 % [93 of 149]) had non-durable response. These researchers identified no new long-term or serious adverse events attributed to CCH during follow-up. Anti-clostridial type I collagenase and/or anti-clostridial type II collagenase antibodies were reported for 96 % or more of patients who received 2 or more CCH injections and 82 % who received 1 injection.
- The authors concluded that recurrence rate, which is comparable to other standard treatments, and the absence of long-term adverse events 3 years after initial treatment indicated that CCH is safe and effective treatment for DC. Most successfully treated joints had a contracture well below the threshold for surgical intervention 3 years after treatment. Recurrence rates among successfully treated joints were lower than non-durable response rates among partially corrected joints.
- In a phase IIb, double-blind, randomized, placebo-controlled study, Gelbard and colleagues (2012) examined the safety and effectiveness of collagenase Clostridium histolyticum and assessed a patient reported outcome questionnaire. A total of 147 subjects were randomized into 4 groups to receive collagenase C. histolyticum or placebo (3:1) with or without penile plaque modeling (1:1). Per treatment cycle 2 injections of collagenase C. histolyticum (0.58 mg) were given 24 to 72 hours apart. Subjects received up to 3 cycles at 6-week intervals. When designated, investigator modeling was done 24 to 72 hours after the second injection of each cycle. These researchers evaluated penile curvature by goniometer measurement, patient reported outcomes and adverse event profiles. After collagenase C. histolyticum treatment significant improvements in penile curvature (29.7 % versus 11.0 %, p = 0.001) and patient reported outcome symptom bother scores (p = 0.05) were observed compared to placebo.
- In modeled subjects 32.4 % improvement in penile curvature was observed in those on collagenase C. histolyticum compared to 2.5 % worsening of curvature in those on placebo (p < 0.001). Those treated with collagenase C. histolyticum who underwent modeling also

showed improved Peyronie disease symptom bother scores (p = 0.004). In subjects without modeling there were minimal differences between the active and placebo cohorts. Most adverse events in the collagenase C. histolyticum group occurred at the injection site and were mild or moderate in severity. No treatment related serious adverse events were reported. The authors concluded that collagenase C. histolyticum treatment was well-tolerated. Moreover, they noted significant improvement in penile curvature and patient reported outcome symptom bother scores, suggesting that this may be a safe, non-surgical alternative for Peyronie disease.

- Gelbard et al (2013) stated that IMPRESS (Investigation for Maximal Peyronie's Reduction Efficacy and Safety Studies) I and II examined the clinical safety and effectiveness of collagenase C. histolyticum intra-lesional injections in subjects with Peyronie disease. Co-primary outcomes in these identical phase III randomized, double-blind, placebo controlled studies included the percent change in the penile curvature abnormality and the change in the Peyronie disease questionnaire symptom bother score from baseline to 52 weeks. IMPRESS I and II examined collagenase C. histolyticum intra-lesional injections in 417 and 415 subjects, respectively, through a maximum of 4 treatment cycles, each separated by 6 weeks. Men received up to 8 injections of 0.58 mg collagenase C. histolyticum that are 2 injections per cycle separated by approximately 24 to 72 hours with the second injection of each followed 24 to 72 hours later by penile plaque modeling.
- Men were stratified by baseline penile curvature (30 to 60 versus 61 to 90 degrees) and randomized to collagenase C. histolyticum or placebo 2:1 in favor of the former. Post hoc meta-analysis of IMPRESS I and II data revealed that men treated with collagenase C. histolyticum showed a mean 34 % improvement in penile curvature, representing a mean +/- SD -17.0 +/- 14.8 degree change per subject, compared with a mean 18.2 % improvement in placebo treated men, representing a mean -9.3 +/- 13.6 degree change per subject (p <0.0001). The mean change in Peyronie disease symptom bother score was significantly improved in treated men versus men on placebo (-2.8 +/- 3.8 versus -1.8 +/- 3.5, p = 0.0037). Three serious adverse events (corporeal rupture) were surgically repaired. The authors concluded that IMPRESS I and II supported the clinical safety and effectiveness of collagenase C. histolyticum for the physical and psychological aspects of Peyronie disease.
- On December 6, 2013, the FDA approved a new use for Xiaflex (collagenase clostridium histolyticum) as the first FDA-approved medicine for the treatment of Peyronie's disease. A treatment course for Peyronie's disease consists of a maximum of 4 treatment cycles. Each treatment cycle consists of 2 Xiaflex injection procedures (in which Xiaflex is injected directly into the collagen-containing structure of the penis) and 1 penile modeling procedure performed by the health care professional. The safety and effectiveness of Xiaflex for the treatment of Peyronie's disease were established in 2 randomized double-

blind, placebo-controlled studies in 832 men with Peyronie's disease with penile curvature deformity of at least 30 degrees. Participants were given up to 4 treatment cycles of Xiaflex or placebo and were then followed 52 weeks.

- Xiaflex treatment significantly reduced penile curvature deformity and related bothersome effects compared with placebo. The most common adverse reactions associated with use of Xiaflex for Peyronie's disease include penile hematoma, penile swelling and penile pain.
- According to the FDA, when prescribed for the treatment of Peyronie's disease, Xiaflex is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) because of the risks of serious adverse reactions, including penile fracture (rupture of one of the penile bodies within the penile shaft, also known as corporal rupture) and other serious penile injury. Xiaflex for the treatment of Peyronie's disease should be administered by a health care professional who is experienced in the treatment of male urological diseases. The REMS requires participating health care professionals to be certified within the program by enrolling and completing training in the administration of Xiaflex treatment for Peyronie's disease. The REMS also requires health care facilities to be certified within the program and ensure that Xiaflex is dispensed only for use by certified health care professionals.

References

1. Badalamente MA, Hurst LC. Enzyme injection as nonsurgical treatment of Dupuytren's disease. J Hand Surg Am. 2000;25(4):629-636
2. Badalamente MA, Hurst LC, Hentz VR. Collagen as a clinical target: Nonoperative treatment of Dupuytren's disease. J Hand Surg Am. 2002;27(5):788-798.
3. Trojian TH, Chu SM. Dupuytren's disease: diagnosis and treatment. Am Fam Physician. 2007;76(1):86-89
4. Swartz WM, Lalonde DH. MOC-PS(SM) CME article: Dupuytren's disease. Plast Reconstr Surg. 2008;121(4 Suppl):1-10.
5. Jordan GH. The use of intralesional clostridial collagenase injection therapy for Peyronie's disease: A prospective, single-center, non-placebo-controlled study. J Sex Med. 2008;5(1):180-187.
6. Hurst LC, Badalamente MA, Hentz VR, et al. Injectable collagenase clostridium histolyticum for Dupuytren's contracture. N Engl J Med. 2009;361(10):968-979.
7. U.S. Food and Drug Administration. FDA approves Xiaflex for debilitating hand condition. FDA News. Silver Spring, MD; FDA; February 2, 2010. Available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm199736.htm. Accessed February 12, 2010.

8. Auxilium Pharmaceuticals, Inc. Xiaflex (collagenase clostridium histolyticum). Prescribing Information. Malvern, PA; Auxilium; February, 2010. Available at: http://www.xiaflex.com/docs/pi_medguide_combo.pdf. Accessed February 12, 2010.
9. Azzopardi E, Boyce DE. Clostridium histolyticum collagenase in the treatment of Dupuytren's contracture. Br J Hosp Med (Lond). 2012;73(8):432-436.
10. Sanjuan Cervero R, Franco Ferrando N, Poquet Jornet J. Use of resources and costs associated with the treatment of Dupuytren's contracture at an orthopedics and traumatology surgery department in Denia (Spain): Collagenase clostridium hystolyticum versus subtotal fasciectomy. BMC Musculoskelet Disord. 2013;14:293.
11. Atroshi I, Strandberg E, Lauritzson A, et al. Costs for collagenase injections compared with fasciectomy in the treatment of Dupuytren's contracture: A retrospective cohort study. BMJ Open. 2014;4(1):e004166.
12. Peimer CA, Blazar P, Coleman S, et al. Dupuytren contracture recurrence following treatment with collagenase clostridium histolyticum (CORDLESS study): 3-year data. J Hand Surg Am. 2013;38(1):12-22.
13. Gelbard M, Lipshultz LI, Tursi J, et al. Phase 2b study of the clinical efficacy and safety of collagenase Clostridium histolyticum in patients with Peyronie disease. J Urol. 2012;187(6):2268-2274.
14. 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;190(1):199-207.
15. U.S. Food and Drug Administration (FDA). FDA approves first drug treatment for Peyronie's disease. FDA News. Silver Spring, MD: FDA; December 6, 2013. Available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm377849.htm?source=govdelivery&utm_medium=email&utm_source=govdelivery. Accessed December 9, 2013.

Reviewed by a Board Certified Internist
Reviewed by David Evans, MD, Medical Director, Active Health Management- May 2016

Codes

CPT® or HCPCS: 20527, 26040, 26341, 77401, J0775