Clinical Policy Bulletin: Dupuytren's Contracture Treatments

Aetna considers collagenase clostridium histolyticum (Xiaflex) injections medically necessary for the treatment of adults with Dupuytren's contracture with a palpable cord.

Aetna considers collagenase clostridium histolyticum injections experimental and investigational for all other indications (e.g., uterine fibroids; except for Peyronie's disease -- see CPB 0007 - Erectile Dysfunction) because its effectiveness other than the one listed above has not been established.

Aetna considers percutaneous needle aponeurotomy (also known as percutaneous needle fasciotomy) medically necessary for the treatment of adults with Dupuytren's contracture with a palpable cord.

Aetna considers percutaneous needle aponeurotomy in combination with lipografting experimental and investigational for the treatment of adults with Dupuytren's contracture because the effectiveness of this approach has not been established.

Aetna considers ortho-voltage radiation medically necessary for the treatment of early-stage Dupuytren's contracture (stage N, N/I). (Note: stage N: nodules/cords, no extension deficit = flexion deformity; stage N/I: less than or equal to 10 degrees deficit).

Aetna considers extracorporeal shock wave therapy for prevention of the progression as well as for treatment of Dupuytren's contracture experimental and investigational because its effectiveness for this indication has not been established.

Aetna considers night-time splinting for all individuals after fasciectomy or dermofasciectomy for Dupuytren's contracture experimental and investigational (unless extension deficits re-occur) because its effectiveness for this indication has not been established.

Notes: Injections of Xiaflex may be administered up to 3 times per cord at approximately 4-week intervals. Up to 2 cords may be injected at a time. If members have other cords with contractures of metacarpophalangeal (MCP) or proximal interphalangeal (PIP) joints, these cords should be injected in sequential order.

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
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, 1,200, 2,400, 4,800, and 9,600 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. Up to two cords may 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.

Another treatment of Dupuytren's contracture (DC) is injection of steroids into the nodule; and has been shown to reduce the need for surgery. Surgical referral should be made when MCP joint contracture reaches 30 degrees or when PIP joint contracture occurs at any degree. In-office percutaneous needle aponeurotomy is an alternative to surgery (Trojian and Chu, 2007).

In a review on percutaneous needle aponeurotomy, Foucher and colleagues (2003) reviewed the charts of 211 patients treated consecutively on 261 hands and 311 fingers to assess the rate of post-operative complications. The first 100 patients were evaluated with a mean follow-up of 3.2 years to assess the rate of recurrences and extension of the disease. In the whole group the mean age was 65 years and delay between onset and treatment was 6 years. Division of the cords were performed only in the palm in 165 cases, in the palm and finger in 111 and purely in the finger in 35. Complications
were scarce without infection or tendon injury but 1 digital nerve was found injured during a second procedure. Post-operative gain was prominent at MCP joint level (79 % versus 65 % at interphalangeal level). The re-operation rate was 24 %. In the group assessed at 3.2 years follow-up, the recurrence rate was 58 % and disease “activity” 69 %. Fifty-nine hands need further surgery. The ideal indication for this simple and reliable technique is an elderly patient with a bowing cord and predominant MP contracture.

Cheng et al (2008) reviewed the safety and effectiveness of needle aponeurotomy for DC in Chinese patients. A total of 7 men and 1 woman aged 50 to 80 (mean of 67) years underwent needle aponeurotomy for DC. Five were manual workers and the other 3 were retired. Their chief complaints were difficulty moving the fingers, clumsiness of the hand, and occasional pain in the palm. No patient had any family history of DC. A total of 41 points were released in 13 fingers (3 middle, 3 ring, and 7 little). Immediately after release, the mean flexion contracture correction of the MCP and PIP joints were 50 (from 50 to 0) and 35 (from 46 to 11) degrees, respectively. At 22-month follow-up, the mean residual flexion contracture of both joints were 12 and 27 degrees; the corresponding long-term improvements were 70 and 41 %, respectively. No patient had a wound complication or neurovascular injury. All had a normal score for Disabilities of the Arm, Shoulder, and Hand. The authors concluded that for Chinese patients with DC, needle aponeurotomy is safe and effective. Long-term correction is better maintained in MCP than PIP joints (70 % versus 41 %).

Lellouche (2008) stated that DC or Dupuytren's disease of the hand is the retraction of the palmar aponeurosis. Its course is progressive and leads to an irreducible flexion deformity of one or more fingers. Early diagnosis is necessary for the table test, which determines the need for treatment. Needle aponeurotomy should be the first option treatment. This minimally invasive out-patient procedure minimizes sick leave and does not require immobilization or physical therapy. Several studies confirmed the short-term and intermediate-term effectiveness of this treatment and the minimal side effects when performed by experienced operators. Multiple procedures for extensive disease (several knots) can be performed in the hospital. Close medical and surgical collaboration is necessary for treatment of severe forms, treatment failures, and multiple recurrences.

Manet and associates (2011) stated that DC is a retractile fibrosis of the superficial palmar aponeurosis of the hand, resulting in a progressive and fixed flexion of the fingers that may result in severe limitation of hand function. It affects several millions of people in Europe and North America. Risk factors are genetic and sometimes related to mellitus diabetes. There is no spontaneous remission. Until recently, surgery was the only treatment, but now needle aponeurotomy emerges as a therapeutic alternative. It should be performed as first-line treatment by a trained practitioner. Short-term and long-term results of needle aponeurotomy appear identical to those of surgery, with milder complications. It is indicated in palmar, palmo-digital, as well as in strictly digital forms of the disorder.

Guidance from the National Institute for Clinical Excellence (NICE, 2004) concluded: "Current evidence on the safety and efficacy of needle fasciotomy for Dupuytren’s contracture appears adequate to support the use of the procedure, provided that normal arrangements are in place for consent, audit and clinical governance." The guidance explained that the main benefit offered by this procedure is a short-term reduction in the degree of contracture. The guidance stated that the evidence shows that the recurrence rate is approximately 50 % at 3 to 5 years and seems to depend on the severity of the disease. The guidance stated that some data suggest that individuals with less severe disease or with metacarpophalangeal joint contracture benefited most from this procedure.

Prophylactic external beam radiation therapy (RT) has been reported to prevent disease progression in early-stage DC.

Keilholz et al (1996) evaluated initial response, long-term outcome, as well as treatment toxicity of RT for the prevention of disease progression in early-stage DC. A total of 96 patients (142 hands) received ortho-voltage RT, which consisted of 2 courses with daily fractionation of 5 x 3 Gy (total dose of 30 Gy) separated by a 6-week interval. The extent of disease was staged according to the
Tubiana's classification. Initial evaluation was performed 3 months after completion of RT; long-term outcome was analyzed at last follow-up. The mean follow-up was 6 +/- 2 (range of 1 to 12) years. Fifty-seven patients with a minimum follow-up of 5 (median 7.5; mean of 9.5 to 12) years were separately evaluated for long-term outcome (i.e., prevention of disease progression). Acute and late treatment toxicity was assessed using the Radiation Therapy Oncology Group/EORTC criteria. According to stage, 130 cases (92 %) remained stable at 3 months follow-up, 10 improved (7 %), and 2 progressed (1 %). An objective reduction of symptomatic cords and nodules was achieved in 107 cases (75 %) at 3 months follow-up. Moreover, 87 % of the patients reported a subjective relief of symptoms. In long-term follow-up, only 16 of 142 cases (11 %) had progressed according to stage. In the group with minimum follow-up 5 years (n = 57), 44 patients (77 %) experienced no disease progression, whereas 13 progressed (23 %) inside [8 cases (14 %)] or outside [5 cases (9 %)] of the RT field. Most failures could have been avoided with appropriate choice of larger safety margins included in the treated portals; however, the failures outside were still amenable for another RT course. The authors concluded that RT is effective to prevent disease progression for early-stage DC, which helps to avoid an otherwise necessary surgical procedure that is performed in advanced stages of DC.

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-up (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 analysis, Betz et al (2010) reported the long-term outcome and late toxicity of RT to prevent disease progression in patients with early-stage DC. A total of 135 patients (208 hands) were irradiated with ortho-voltage (120 kV; 20 mA; 4-mm Al filter) in 2 courses with 5 daily fractions of 3.0 Gy to a total dose of 30 Gy; separated by a 6- to 8-week interval. The extent of disease was described according to a modified Tubiana's classification. Long-term outcome was analyzed at last follow-up
with a median follow-up of 13 years (range of 2 to 25 years). Late treatment toxicity and objective reduction of symptoms as change in stage and numbers of nodules and cords were evaluated and used as evidence to assess treatment response. According to the individual stages, 123 cases (59 %) remained stable, 20 (10 %) improved, and 65 (31 %) progressed. In stage N 87 % and in stage N/I 70 % remained stable or even regressed. In more advanced stages, the rate of disease progression increased to 62 % (stage I) or 86 % (stage II). A total of 66 % of the patients showed a long-term relief of symptoms (i.e., burning sensations, itching and scratching, pressure and tension). Radiotherapy did not increase the complication rate after surgery in case of disease progression and only minor late toxicity (dry desquamation, skin atrophy) could be observed in 32 % of the patients. There was no evidence for a second malignancy induced by RT. The authors concluded that after a mean follow-up of 13 years, RT is effective in prevention of disease progression and improves patients’ symptoms in early-stage DC (stage N, N/I). In case of disease progression after RT, a "salvage" operation is still feasible.

Guidance from the National Institute for Health and Clinical Excellence (NICE, 2010) concluded: "Evidence on the safety of radiation therapy for early Dupuytren's disease is limited in quantity but does not raise any serious safety concerns. The evidence on efficacy is limited in quantity and there is uncertainty about the natural history of early Dupuytren's disease, which makes evaluation of the effect of the procedure difficult."

Knobloch et al (2011) noted that Dupuytren's disease is a progressive disease due to unknown causal agents or genetics. An epidemiological analysis of 566 cases in North Germany estimated that around 1.9 million Germans are suffering from Dupuytren's disease. Beside Dupuytren's disease, there are a number of further less common forms of progressive fibromatosis, such as knuckle pads, plantar fibromatosis or Peyronie's disease. Surgery in plantar fasciectomy yields to a 60 % recurrence rate depending on the extent of the plantar fasciectomy. Peyronie's disease of the penis affects middle-aged men between 40 and 60 years with penile pain, curvature during erection and potential erectile dysfunction. In a randomized controlled trial (RCT) in Peyronie's disease 2,000 focused extracorporeal shock waves reduced pain significantly and improved erectile function and quality of life. These researchers hypothesize that focused extracorporeal shock wave therapy (ESWT) is able to reduce Dupuytren's contracture. Given the fact that recurrence rate in Dupuytren's disease is high and unpredictable, ESWT as a non-invasive tool might be applicable both, in primary and secondary prevention of the progression as well as for treatment. As such, these investigators have planned a RCT studying the effect of high-energy focused ESWT on patients suffering Dupuytren's disease with patient-related outcome measures such as the Disabilities of the Arm, Shoulder and Hand (DASH) score and the Michigan Hand Outcome Questionnaire as primary outcome parameters.

In a multi-center, open, randomized controlled trial, Jerosch-Herold et al (2011) evaluated the effect of night splinting on self-reported function, finger extension and satisfaction in patients undergoing fasciectomy or dermofasciectomy for Dupuytren's contracture. A total of 154 patients from 5 regional hospitals were randomized after surgery to receive hand therapy only (n = 77) or hand therapy with night-splinting (n = 77). Primary outcome was self-reported function using the DASH questionnaire. Secondary outcomes were finger range of motion and patient satisfaction. Primary analysis was by intention-to-treat. A total of 148 (96 %) patients completed follow-up at 12 months. No statistically significant differences were observed on the DASH questionnaire (0 to 100 scale: adjusted mean diff. 0.66, 95 % CI: -2.79 to 4.11, p = 0.703), total extension deficit of operated digits (degrees: adjusted mean diff 5.11, 95 % CI: -2.33 to 12.55, p = 0.172) or patient satisfaction (0 to 10 numerical rating scale: adjusted mean diff -0.35, 95 % CI: -1.04 to 0.34, p = 0.315) at 1 year post surgery. Similarly, in a secondary per protocol analysis no statistically significant differences were observed between the groups in any of the outcomes. The authors concluded that no differences were observed in self-reported upper limb disability or active range of motion between a group of patients who were all routinely splinted after surgery and a group of patients receiving hand therapy and only splinted if and when contractures occurred. Given the added expense of therapists' time, thermoplastic materials and the potential inconvenience to patients having to wear a device, the routine addition of night-time splinting for all patients after fasciectomy or dermofasciectomy is not recommended except where
extension deficits re-occur.

Hovius and colleagues (2011) described a novel minimally invasive alternative for Dupuytren disease and its outcome. The procedure consists of an extensive percutaneous aponeurotomy that completely disintegrates the cord and separates it from the dermis. Subsequently, the resultant loosened structure is grafted with autologous lipo-aspirate. After 1 week of post-operative extension splinting, patients are allowed normal hand use and are advised to use night splints for 3 to 6 months. These investigators treated and reported on their experience with 91 patients (99 hands) operated on in Miami and Rotterdam; from 50 patients, the authors reported on goniometry (average follow-up of 44 weeks). The contracture from the PIP joint improved significantly from 61 degrees to 27 degrees, and contracture from the MCP joint improved from 37 degrees to -5 degrees; 94 % of patients returned to normal use of the hand within 2 to 4 weeks and 95 % were very satisfied with the result. No new scars were added, and a supple palmar fat pad was mostly restored. Complications were digital nerve injury in 1 patient, post-operative wound infection in 1 patient, and complex regional pain syndrome in 4 patients. The authors concluded that this new minimally invasive technique shortens recovery time, adds to the deficient subcutaneous fat, and leads to scarless supple skin. By its ability to treat multiple rays, it addresses the abnormality in the entire hand. The procedure is safe and effective, especially for primary cases. Moreover, they stated that comparative prospective randomized studies are currently in process to fully determine the role of percutaneous aponeurotomy plus lipografting in the treatment of Dupuytren contracture.

In a pilot study, Kemler and colleagues (2012) evaluated the effectiveness of post-operative splinting after limited fasciectomy for Dupuytren's disease. A total of 54 patients with a PIP joint flexion contractures of at least 30° were randomized to receive either a 3-month splinting protocol together with hand therapy under the direct supervision of hand therapists, or the same hand therapy alone. Extension deficit of the PIP joint (primary outcome measure), global perceived effect, pain intensity, comfort and complications were assessed at baseline and 1 year after surgery. In an intention-to-treat analysis, the group assigned to splint-plus-hand therapy had a mean reduction of 21° in flexion contracture after 1 year, compared with 29° in the group receiving hand therapy alone (p = 0.1). There was no difference between the groups regarding other parameters. After operative release of a Dupuytren's contracture, a post-operative protocol using a splint and hand therapy was no better than hand therapy alone in minimizing post-operative flexion contractures.

In a single-center RCT, Collis et al (2013) examined the effectiveness of night extension orthoses on finger range of motion and hand function for 3 months following surgical release of Dupuytren contracture. These researchers also determined how well finger extension was maintained in the total sample. They randomized 56 patients to receive a night extension orthosis plus hand therapy (n = 26) or hand therapy alone (n = 30). The primary outcome was total active extension of the operated fingers (degrees). Secondary outcomes were total active flexion of the operated fingers (degrees), active distal palmar crease (cm), grip strength (kg), and self-reported hand function using the Disabilities of the Arm, Shoulder, and Hand questionnaire (0 to 100 scale). There were no statistically significant differences between the no-orthosis and orthosis groups for total active extension or for any of the secondary outcomes. Between the first post-operative measure and 3 months after surgery, 62 % of little fingers had maintained or improved total active extension. The authors concluded that the use of a night extension orthosis in combination with standard hand therapy has no greater effect on maintaining finger extension than hand therapy alone in the 3 months following surgical release of Dupuytren contracture. These findings indicated that the practice of providing every patient with a night extension orthosis following surgical release of Dupuytren contracture may not be justified except for cases in which extension loss occurs after surgery. They stated that their results also challenged clinicians to research ways of maintaining finger extension in a greater number of patients.

Sanjuan Cervero et al (2013) compared the use of direct health resources and costs generated in the treatment of DC using 2 different techniques: (i) subtotal fasciectomy and (ii) infiltration with collagenase clostridium histolyticum (CCH) in regular clinical practice. Observational, retrospective study based on data from the computerized clinical histories of 2 groups of patients: (i) those treated
surgically using a 1- or 2-digit subtotal fasciectomy technique (FSC) and (ii) those treated with CCH infiltration, monitored in regular clinical practice from February 2009 to May 2012. Demographic (age, sex), clinical (number of digits affected and which ones) and use of resources (hospitalizations, medical visits, tests and drugs) data were collected. Resource use and associated costs, according to the hospital’s accounting department, were compared based on the type of treatment from Spain’s National Health Service. A total of 91 patients (48 (52.8 %) in the FSC group) were identified. The average age and number of digits affected was 65.9 (9.2) years and 1.33 (0.48) digits affected in the FSC group, and 65.1 (9.7) years and 1.16 (0.4) digits in the CCH group. Overall, the costs of treating DC with subtotal FSC amount to €1,814 for major ambulatory surgery and €1,961 with hospital stay including admission, surgical intervention (€904), examinations, dressings and physiotherapy. As to collagenase infiltration, costs amount to €952 (including minor surgery admission, vial with product, office examination and dressings). Finally, comparing total costs for treatments, a savings of €388 is estimated in favor of CCH treatment in the best-case scenario (patient under MAS system with no need for physiotherapy) and €1,008 in the worst-case scenario (patient admitted to hospital needing subsequent physiotherapy), implying a savings of 29 % and 51 %, respectively. The authors concluded that this study demonstrated that treating patients with DC by injection with CCH generated a total savings of 29 % and 51 % (€388 and €1008) compared with fasciectomy at the time of treatment. Moreover, they stated that long-term evolution of CCH treatment is uncertain and the recurrence rate unknown.

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 30° 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 = 0° to 5° contracture after CCH administration) was defined as 20° 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 20° or more from baseline contracture but not to 0° to 5°) for nondurable response, also defined as 20° 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 0° to 5° 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.

**Uterine Fibroids:**

Jayes and colleagues (2016) tested the hypothesis that a highly purified collagenase clostridium histolyticum will digest interstitial collagen in uterine fibroids and reduce their stiffness and evaluated the feasibility that clostridium histolyticum collagenase can be developed into an alternative treatment for fibroids. A secondary objective was to describe the collagen content of the fibroid tissue. Fibroid tissue cubes (1-cm³; n = 154) were cut from 17 uterine fibroids that were obtained from 7 consented subjects undergoing scheduled hysterectomies. Tissue cubes were injected with diluent, placebo, or highly purified collagenase clostridium histolyticum (0.05, 0.1, or 0.2 mg per cube) and incubated at 37°C for 24, 48, 72, or 96 hours. At each time-point, 6 non-injected control cubes were also evaluated. Tissue cubes were photographed before and after incubation. Myometrial samples (n = 21) were also evaluated. Stiffness was quantified through rheometry by measuring complex shear moduli of the tissues. Percent fibrosis was determined by computerized analysis of Masson-Trichrome stained slides. Digestion of collagen fibrils was confirmed by transmission electron microscopy. Fibrosis in untreated fibroids ranged from 37% to 77% reflecting the collagen-rich nature of these tumors. After treatment with collagenase for 96 hours, fibrosis ranged from 5.3% to 2.4%. Transmission electron microscopy confirmed complete digestion of collagen fibrils. Tissue stiffness was reduced with all 3 doses of collagenase treatment and at all 4 time-points. Longer incubation times with collagenase caused greater reduction in stiffness and treated cubes lost their cuboidal shape and had gelatinous/liquefied centers. At 96 hours stiffness in tissues treated with the lowest dose was reduced to 966 ± 106 Pascal compared to diluent-treated control at the same time (5,323 ± 903 Pascal; p < 0.0001; by analysis of variance with Tukey-Kramer). The authors concluded that uterine fibroids have a high content of collagen that can be effectively digested by highly purified collagenase clostridium histolyticum resulting in reduced tissue stiffness. Loss of stiffness may decrease bulk symptoms in-vivo and possibly lead to shrinkage of fibroids through changed mechano-transduction leading ultimately to reduced fibroid symptoms of pain and bleeding. The authors stated that clinical trials are needed to evaluate safety and effectiveness of clostridium histolyticum collagenase including the rate of regrowth of fibroids. They noted that the data of this study provided a strong rationale for using this purified collagenase in clinical trials as a local treatment for women with fibroids.

**Appendix**

The Xiaflex prescribing information recommends the following dosing for Dupuytren’s contracture:

- Xiaflex should be administered by a healthcare provider experienced in injection procedures of the hand and in the treatment of Dupuytren’s contracture.
- Reconstitute Xiaflex lyophilized powder with only the supplied diluent prior to use.
- Inject 0.58 mg of Xiaflex into each palpable Dupuytren’s cord with a contracture of a 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 a treatment visit.
- Approximately 24 to 72 hours following an 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 2 cords in the same hand at a treatment visit. If a patient has other cords with
contractures, inject those cords at another treatment visit.


CPT Codes / HCPCS Codes / ICD-10 Codes

Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by “+”:

CPT codes covered if selection criteria are met:

20527  Injection, enzyme (eg, collagenase), palmar fascial cord (ie, Dupuytren's contracture)
26040  Fasciotomy, palmar (eg, Dupuytren's contracture_
26341  Manipulation, palmar fascial cord (ie, Dupuytren's cord), post enzyme injection (eg, collagenase), single cord
77401  Radiation treatment delivery, superficial and/or ortho voltage, per day

CPT codes not covered for indications listed in the CPB (not all-inclusive):

0019T  Extracorporeal shock wave involving musculoskeletal system, not otherwise specified, low energy
0101T  Extracorporeal shock wave involving musculoskeletal system, not otherwise specified, high energy
15770  Graft; derma-fat-fascia
28890  Extracorporeal shock wave, high energy, performed by a physician or other qualified health care professional, requiring anesthesia other than local, including ultrasound guidance, involving the plantar fascia

Other CPT codes related to the CPB:

20550  Injection(s); single tendon sheath, or ligament, aponeurosis (eg, plantar "fascia")

HCPCS codes covered if selection criteria are met:

J0775  Injection, collagenase clostridium histolyticum, 0.01 mg

ICD-10 codes covered if selection criteria are met:

M72.0  Palmar fascial fibromatosis [adults with Dupuytren's contracture with a palpable cord]

ICD-10 codes not covered for indications listed in the CPB (not all-inclusive):

D25.0 - D25.9  Leiomyoma of uterus

The above policy is based on the following references:

32. Auxilium Pharmaceuticals, Inc. Xiaflex (collagenase clostridium histolyticum) for injection, for intralesional use. Prescribing Information. PL-0108-001.g. Malvern, PA; Auxilium; revised July 2015.
AETNA BETTER HEALTH® OF PENNSYLVANIA

Amendment to
Aetna Clinical Policy Bulletin Number: 0800 Dupuytren's Contracture Treatments

There are no amendments for Medicaid.

www.aetnabetterhealth.com/pennsylvania revised 08/05/2016