Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

Nonprofit corporations and independent licensees of the Blue Cross and Blue Shield Association

***Current Policy Effective Date: 11/1/12**
(See policy history boxes for previous effective dates)

Title: Collagenase Clostridium Histolyticum (e.g., Xiaflex®) for Injection

Description / Background

Collagenases are enzymes that digest native collagen. They are being evaluated for treatment of fibroproliferative disorders such as Dupuytren's contracture and Peyronie's disease. Clostridial collagenase is a bacterial collagenase derived from *Clostridium histolyticum*. Treatment of Dupuytren's contracture consists of injection of collagenase into the cord followed by manipulation of the finger if contracture persists. Injection may be done up to three times at four-week intervals.

Injection with clostridial collagenase is intended to provide a non-operative treatment option for fibroproliferative disorders. Fibrotic tissue disorders, characterized by excessive collagen deposits, can affect the musculoskeletal system, causing pain and limitation of movement and reduction of joint range of motion. Dupuytren's disease and adhesive capsulitis are such musculoskeletal disorders. Peyronie's disease is another example.

The mechanisms that contribute to the pathology of Dupuytren's disease, adhesive capsulitis and Peyronie's diseases are poorly understood. In Dupuytren's disease, collagen deposition results in nodules and cords in the palm and fingers, resulting in pitting of the overlying cutis and flexion contractures. The standard of care for Dupuytren's disease is surgery, most commonly open fasciectomy. Other surgical procedures are percutaneous fasciotomy and needle fasciotomy. Surgery is recommended in patients with functional impairment and metacarpophalangeal-joint contractures of 30 degrees or more. There is no effective pharmacotherapy.

Adhesive capsulitis or "frozen shoulder" is treated with physiotherapy and mobilization in combination with analgesics or nonsteroidal anti-inflammatory drugs. Corticosteroid injection is used with caution. The prevalence of Dupuytren's disease and adhesive capsulitis is estimated at three to six percent and two to three percent, respectively, in the general population and

increases with advancing age. Both conditions are more common in patients with diabetes or thyroid disease. Dupuytren's disease is more common in men and adhesive capsulitis more common in women.

Peyronie's disease is the development of abnormal scar tissue, or plaques, in the tunica albuginea layer of the penis causing distortion, curvature and pain usually during erection. It occurs in three to nine percent of men, most commonly between the ages of 45 and 60. In some cases, plaque does not cause severe pain or curvature, and the condition resolves on its own. In severe cases, erectile dysfunction can occur. The goal of treatment is to reduce pain and maintain sexual function.

Regulatory Status:

In February 2010, the U.S. Food and Drug Administration (FDA) approved Auxilium Pharmaceutical Inc.'s biologics license application for clostridial collagenase histolyticum (Xiaflex) for treatment of adult patients with Dupuytren's contracture with a palpable cord. The FDA labeling for Xiaflex states that up to three injections at four week intervals may be given into a palpable Dupuytren's cord with a contracture of a metacarpophalangeal (MP) joint or a proximal interphalangeal (PIP) joint. This enzyme weakens the cord which then can be pulled and mechanically broken. This is an office-based procedure, and anesthesia is not required.

Medical Policy Statement

The safety and efficacy of injections of collagenase clostridium histolyticum for the treatment of Dupuytren's contracture have been established. It is a useful therapeutic option for patients meeting patient selection criteria.

Inclusionary and Exclusionary Guidelines (Clinically based guidelines that may support individual consideration and pre-authorization decisions)

Inclusions

Collagenase clostridium histolyticum (i.e., Xiaflex™) for the treatment of Dupuytren's contracture is considered established if ALL of the following criteria are met:

- The individual is 18 years of age or older
- A finger flexion contracture with a palpable cord of at least one finger (other than the thumb) involving the metacarpophalangeal (MP) joint or the proximal interphalangeal (PIP) joint
- Functional impairment as a result of the contracture

Collagenase clostridium histolyticum injections should only be administered by a surgeon with training and experience in performing procedures on the hand and treating Dupuytren's contracture.

Exclusions

- Use of collagenase clostridium histolyticum (i.e., Xiaflex) for the treatment of other conditions, including but not limited to Peyronie's disease or adhesive capsulitis.

- Patients not meeting inclusionary guidelines.

CPT / HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure)*

Established codes:

J0775 20527 26341

Other codes (investigational, not medically necessary, etc.):

N/A

Rationale

A number of nonsurgical interventions for fibroproliferative disease have been studied. Investigations of a potential role for injectable clostridial collagenase have been ongoing for over 20 years. FDA approval has recently been granted for treatment of Dupuytren's contracture with a palpable cord. Some authors include collagenase among standard injection therapies for Peyronie's disease. Use of the material for treatment of conditions other than Dupuytren's contracture is an off-label application.

Dupuytren's Disease (Dupuytren's Contracture)
In 2009, Hurst and colleagues published a randomized, double-blind placebo-controlled, multicenter trial (16 sites) of collagenase clostridium histolyticum for Dupuytren's contracture with 308 subjects with joint contractures of 20 degrees or more. Joints were stratified according to type (MP or PIP) and severity of contracture and randomly assigned in a two to one ratio to receive up to three injections of either collagenase or placebo in the contracted collagen cord at 30-day intervals. Secondary and tertiary joints were identified for possible subsequent injections. Joints were manipulated one day after injection when necessary. The primary endpoint was reduction in contracture to zero to five degrees of full extension 30 days after last injection. Twenty-six secondary endpoints were also evaluated. Recurrence of contracture was defined as an increase in joint contracture to at or greater than 20 degrees and was considered an adverse event. Efficacy results were based on 306 primary joints; 203 injected with collagenase and 103 injected with placebo. In the collagenase-treated group, 130 of 203 (64 percent) cords met the primary endpoint versus seven of 103 (6.8 percent) placebo-injected cords. More than half of the collagenase-injected joints that did not meet the primary end point did not receive the maximum allowable number of injections, most commonly because a cord could not be palpated or the patient was satisfied with the result. Median time to reach the primary end point for collagenase-treated joints was 56 days. At the 90-day visit, there was no recurrence of contracture in collagenase-treated primary joints that had reached the primary end point.

When analyzed by joint type, more collagenase-treated joints achieved the primary endpoint than placebo (MP 76.7 percent vs. 7.2 percent, respectively, and PIP joint 40.9 percent vs. 5.9 percent, respectively). The mean change in contracture from baseline to 30 days after last injection was 48.0 to 7.2 degrees in the collagen-injected MP joints and 45.4 to 43.1 degrees in the placebo-injected MP joints. Thirty days after last injection, 84.7 percent of collagenase-

injected joints versus 11.7 percent of placebo-injected joints showed clinical improvement. Results were better in MP joints than in PIP joints: 94.0 percent versus 67.1 percent in the collagenase group and 11.6 percent versus 11.8 percent in the placebo group. Overall, 96.6 percent of patients who received collagenase reported at least one treatment-related adverse event. They had significantly more injection and manipulation-related events, such as contusion, hemorrhage, injection-site pain, upper extremity pain and lymphadenopathy, than patients who received placebo injection. Most events were mild or moderate in intensity. However, 20 patients in the collagenase group and two in the placebo group reported events that were severe in intensity. Three severe adverse events were considered to be treatment related; a case of complex regional pain syndrome and two tendon ruptures, both requiring surgical procedures.

Peyronie's Disease

Authors of a 2007 systematic review of plaque injection therapy (Russell, et al.) included two studies of collagenase in their analysis. Both papers reported positive treatment outcomes. One study was rated, according to the Oxford Centre for Evidence-Based Medicine criteria, as level two (randomized controlled trial [RCT] with low power or less than 80 percent follow-up/retention or good-quality, randomized prospective cohort study), and the other level (case series or poor-quality cohort or case-control study). Agents used in the other 19 studies reviewed were corticosteroid, verapamil and interferon. In a 1985 paper on a series of 31 men treated, 20 showed improvement. Pain was eliminated in 13 of 14 patients who experienced pain before treatment. One small corporeal rupture at the injection site was reported in one patient. No significant adverse events were reported in 9.8 months of follow-up.

In a 1993 randomized, placebo-controlled, double-blind study with 49 subjects reported by the same author and other colleagues, the effects of collagenase and placebo on plaque size and penile deformity were investigated. For the group as a whole, treatment with collagenase was significantly more effective. Patients with lesser deformity responded more favorably to treatment.

In 2008, Jordan reported on a series of 25 patients with well-defined plaque treated with three intralesional injections of clostridial collagenase over seven to10 days with repeat treatment at three months. Primary end-points were changes from baseline in deviation angle and plaque size. Significant decreases from baseline were achieved in the mean deviation angle at months three and six; plaque width at months three, six and nine; and plaque length at months three and six. More than 50 percent of patients in this series considered themselves "very much improved" or "much improved" at all timepoints in the study, and the drug was generally well tolerated. An industry-sponsored, placebo-controlled trial is underway.

Adhesive capsulitis

No studies including patients with adhesive capsulitis were identified in the literature search.

In conclusion, the evidence from one large clinical trial suggests that injectable clostridial collagenase provides short-term release of contracture in Dupuytren's disease. However, longer-term recurrence rates are not reported. A comparison of overall outcomes compared to surgical intervention may also be useful. Potentially serious adverse events also warrant further investigation. Small trials demonstrated short-term improvement in patients with Peyronie's disease. Larger trials directly comparing outcomes with current treatment options are required.

Government Regulations

National:

There is no national coverage determination.

Local:

Wisconson Physician Services (WPS)
LCD ID Number - L30153
LCD Title Injections - Tendon, Ligament, Ganglion Cyst, Tunnel Syndromes and Morton's Neuroma, Original Determination Effective Date - for services performed on or after 10/16/2009, Revision Effective Date - For services performed on or after 01/01/2012

Xiaflex TM (collagenase clostridium histolyticum) for Dupuytren's contracture
Effective February 2, 2010, The Food and Drug Administration (FDA) granted approval for Xiaflex TM (collagenase clostridium histolyticum). This collagenase is indicated for adult patients suffering from Dupuytren's contracture with a palpable cord. The packaging insert indicates health care providers experienced with hand injection procedures and the treatment of Dupuytren's contracture should administer Xiaflex into a palpable Dupuytren's cord with contracture of the metacarpophalangeal or proximal interphalangeal joint. Injections may be administered up to three times per cord if necessary at approximately four-week intervals. Only one cord should be injected at a time.

Treatment with Collagenase clostridium histolyticum Xiaflex^{TM} is only indicated for Dupuytren's contractures, ICD-9 code 728.6 (Contracture of palmar fascia). (20527, 26341 and J0775).

Michigan Department of Community Health:

There is no specific information published by MDCH on this procedure. There are fees listed for procedure codes 20527, 26341 and J0775.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

N/A

References

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19. Wisconsin Physician Services (WPS) Medicare, LCD ID Number - L30153, “Injections - Tendon, Ligament, Ganglion Cyst, Tunnel Syndromes and Morton's Neuroma,” Accessed from http://www.wpsmedicare.com/part_b/policy/active/local/l30153_ms007.shtml, Date accessed 7/10/12.
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The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through July 10, 2012, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
5/1/11	3/17/11	3/3/11	Joint policy established
11/1/11	10/11/11	11/9/11	Status of Xiaflex injection changed from experimental and investigational to “established” for selected patients with Dupuytren’s contracture. All other uses for Xiaflex are considered experimental and investigational. Effective date established as 11/1/11.
11/1/12	8/21/12	8/21/12	This policy is replaced as there is a pharmacy policy on this topic. Inquiries on this topic should be directed to the pharmacy department.

Next Review Date: No further reviews. Inquiries on this topic should be directed to the pharmacy department.

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: COLLAGENASE CLOSTRIDIUM HISTOLYTICUM (E.G., XIAFLEX®)

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Covered; criteria apply.
BCNA (Medicare Advantage)	Covered. Follow Medicare guidelines: Effective February 2, 2010, The Food and Drug Administration (FDA) granted approval for Xiaflex TM (collagenase clostridium histolyticum). This collagenase is indicated for adult patients suffering from Dupuytren's contracture with a palpable cord. The packaging insert indicates health care providers experienced with hand injection procedures and the treatment of Dupuytren's contracture should administer Xiaflex into a palpable Dupuytren's cord with contracture of the metacarpophalangeal or proximal interphalangeal joint. Injections may be administered up to three times per cord if necessary at approximately four-week intervals. Only one cord should be injected at a time. Treatment with Collagenase clostridium histolyticum XiaflexTM is only indicated for Dupuytren's contractures, ICD-9 code 728.6 (Contracture of palmar fascia). (20527, 26341 and J0775).
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.
Blue Cross Complete of Michigan	Covered. Follows Medicare guidelines

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.