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Injectable Clostridial Collagenase for Fibroproliferative Disorders

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Disclaimer

Medical policies are a set of written guidelines that support current standards of practice. They are based on current generally accepted standards of and developed by nonprofit professional association(s) for the relevant clinical specialty, third-party entities that develop treatment criteria, or other federal or state governmental agencies. A requested therapy must be proven effective for the relevant diagnosis or procedure. For drug therapy, the proposed dose, frequency and duration of therapy must be consistent with recommendations in at least one authoritative source. This medical policy is supported by FDA-approved labeling and/or nationally recognized authoritative references to major drug compendia, peer reviewed scientific literature and generally accepted standards of medical care. These references include, but are not limited to: MCG care guidelines, DrugDex (IIa level of evidence or higher), NCCN Guidelines (IIb level of evidence or higher), NCCN Compendia (IIb level of evidence or higher), professional society guidelines, and CMS coverage policy.

Carefully check state regulations and/or the member contract.

Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Legislative Mandates

EXCEPTION: For HCSC members residing in the state of Ohio, § 3923.60 requires any group or individual policy (Small, Mid-Market, Large Groups, Municipalities/Counties/Schools, State Employees, Fully-Insured, PPO, HMO, POS, EPO) that covers prescription drugs to provide for the coverage of any drug approved by the U. S. Food and Drug Administration (FDA) when it is prescribed for a use recognized as safe and effective for the treatment of a given indication in one or more of the standard medical reference compendia adopted by the United States Department of Health and Human Services or in medical literature even if the FDA has not approved the drug for that indication. Medical literature support is only satisfied when safety and efficacy has been confirmed in two articles from major peer-reviewed professional medical journals that present data supporting the proposed off-label use or uses

as generally safe and effective. Examples of accepted journals include, but are not limited to, Journal of American Medical Association (JAMA), New England Journal of Medicine (NEJM), and Lancet. Accepted study designs may include, but are not limited to, randomized, double blind, placebo controlled clinical trials. Evidence limited to case studies or case series is not sufficient to meet the standard of this criterion. Coverage is never required where the FDA has recognized a use to be contraindicated and coverage is not required for non-formulary drugs.

Coverage

Injectable clostridial collagenase **may be considered medically necessary** for the treatment of adults with Dupuytren's contracture when ALL of the following criteria are met:

1. A palpable cord; AND
2. A contracture of a metacarpophalangeal (MP) joint or a proximal interphalangeal (PIP) joint.

NOTE 1: Treatment of up to 2 cords or 2 joints in the same hand may be allowed at a treatment visit. If a patient has more than 2 cords in the same hand, those cords should be injected at another visit. A finger extension procedure may be performed approximately 24 to 72 hours following an injection. Injection and finger extension procedures may be administered up to 3 times per cord at approximately 4-week intervals.

Injectable clostridial collagenase **may be considered medically necessary** for the treatment of adult individuals with Peyronie's disease when ALL of the following criteria are met:

1. Palpable penile plaque; AND
2. Objective documentation in the medical record of a penile curvature deformity of at least 30 degrees at start of therapy, as measured using intracavernosal injection (ICI) and goniometer; AND
3. Treatment will be administered in conjunction with a penile modeling procedure (1 to 3 days after injection).

NOTE 2: 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 clostridial collagenase injection procedures and 1 penile modeling procedure.

NOTE 3: The U.S. Food and Drug Administration (FDA) requires provider and patient enrollment in a Xiaflex Risk Evaluation and Mitigation Strategy (REMS) program.

Injectable clostridial collagenase **is considered experimental, investigational and/or unproven** for all other indications including, but not limited to, adhesive capsulitis.

NOTE 4: Please see MED201.030 Sexual Dysfunctions, Assessment and Treatment for additional information on the use of Verapamil for Peyronie's disease.

Policy Guidelines

Subgroups of Individuals
For individuals with Peyronie's Disease, the 2015 American Urological Association clinical practice guidelines noted that clinicians should bear in mind that, based on the inclusion and exclusion criteria for the IMPRESS trials, the use of collagenase treatment in certain subgroups of individuals or clinical situations has not been sufficiently evaluated. These subgroups are individuals with hourglass deformity, ventral curvature, calcified plaque, or plaque located proximal to the base of the penis.

Multiple Injections
For patients with Dupuytren's contracture, physicians should treat no more than 2 joints per hand per treatment visit (this is consistent with U.S. Food and Drug Administration labeling).

Description

Clostridial collagenase is a bacterial collagenase, derived from *Clostridium histolyticum*, which has been evaluated for the treatment of fibroproliferative disorders such as Dupuytren's contracture, Peyronie's disease, and adhesive capsulitis.

Fibroproliferative Disorders
Fibrotic tissue disorders, characterized by excessive collagen deposits, can affect the musculoskeletal system, causing pain and limiting movement and reducing joint range of motion. Examples of fibroproliferative disorders include Dupuytren's disease, Peyronie's disease, and adhesive capsulitis. The mechanisms that contribute to the pathology of fibroproliferative disorders are poorly understood, though likely the etiology is multifactorial and includes genetic, environmental, and immunologic components.

Dupuytren's Disease
Dupuytren's disease is a progressive disorder of the palmar and digital fascia of the hand, leading to flexion deformity in up to 40% of those affected. Prevalence increases with age, from about 12% at age 55 years to 29% at 75 years. (1) Disease that has progressed to the point of limited hand function or digital flexion of 30 degrees or more is generally treated with surgery.

Peyronie's Disease
Peyronie's disease is characterized by deformities, including curvature, shortening, indentation and narrowing in an erect penis. (2) Men with Peyronie's disease may also have erectile dysfunction (ED) and penile pain, along with anxiety and depression. Peyronie's disease occurs most commonly in middle-aged men (45 to 60 years), although up to 10% of cases involve men younger than 40 years; prevalence is estimated to be 9%, though underreporting is likely. Comorbidities associated with Peyronie's disease include diabetes and cardiovascular disease. Patients with early-stage disease may be managed medically, though the effectiveness of many non-surgical treatments is unclear. Later disease can be treated surgically.

Adhesive Capsulitis

The prevalence of adhesive capsulitis is estimated at 2% to 3% in the general population and increases with advancing age. Additionally, adhesive capsulitis is more common in people with diabetes or thyroid disease among women. (3) Adhesive capsulitis is treated with physical therapy and mobilization in combination with analgesics or nonsteroidal anti-inflammatory drugs. Corticosteroid injection is used with caution.

Clostridial Collagenase

Injection with clostridial collagenase is intended to provide a nonoperative treatment option for fibroproliferative disorders. Clostridial collagenase histolyticum is an enzyme produced by the bacterium *Clostridium histolyticum*, which has the physiologic effect of breaking down collagen. It has been developed and marketed pharmacologically as a treatment for disorders associated with collagen overdevelopment.

Regulatory Status

Table 1 lists indications for clostridial collagenase (Xiaflex®; Auxilium Pharmaceuticals [Norristown, PA]) that have been approved by the U.S. Food and Drug Administration (FDA).

Table 1. FDA-Approved Indications for Clostridial Collagenase (Xiaflex®)

Indication	Approved	Indications	Additional Information
Dupuytren's contracture	2010	• Adults with Dupuytren's contracture with a palpable cord. • Up to 3 injections at 4-week intervals into a palpable Dupuytren's cord with a contracture of a metacarpophalangeal or a proximal interphalangeal joint.	• Approval accompanied by REMS. • The manufacturer must: o Evaluate and mitigate risks and serious adverse events. o Instruct health care providers on the procedure to inject Xiaflex and perform finger extension procedures. o Inform patients of potential risks of treatment.
	2014		• Indication expanded: up to 2 joints in the same hand may be treated during a treatment visit.
Peyronie's disease	2013	• Men with a palpable [a] penile plaque and penile curvature >30 degrees.	• Approval accompanied by black box warning of corporal rupture and penile hematoma.

		• A maximum of 4 cycles, each of which consists of 2 Xiaflex injection procedures.	• Only available through a restricted program (Xiaflex REMS), due to risk of corporal rupture. REMS requirements: ○ Prescribers must enroll and complete training in the administration of Xiaflex for the treatment of Peyronie's disease; ○ Health care sites must be certified with the program and ensure that only certified prescribers administer Xiaflex.

[a]Adapted from the Food and Drug Administration (2023). (4)
FDA: Food and Drug Administration; REMS: Risk Evaluation and Mitigation Strategy.

The discussion section of the 2015 American Urological Association guideline for use of clostridial collagenase in Peyronie's disease indicates that the exclusion criteria for the pivotal trials "included severe pain with penile palpation by the clinician, ED (erectile dysfunction) that was unresponsive to PDE5 (phosphodiesterase type 5) inhibitors, and lack of full erectile response to prostaglandin E1 during curvature measurement." (5)

Rationale

Medical policies assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function, including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent 1 or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events

and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Dupuytren's Disease (Dupuytren's Contracture)

Clinical Context and Therapy Purpose

The purpose of administering local clostridial collagenase injection(s) in individuals who have Dupuytren's contracture is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this policy.

Populations

The relevant population of interest is individuals with Dupuytren's contracture. In Dupuytren's disease, collagen deposition in nodules and cords in the palm and fingers results in pitting of the overlying cutis and flexion contractures. The prevalence of Dupuytren's disease is estimated at 8.2% worldwide. (6) The risk factors for this disease include aging (Dupuytren usually occurs after the age of 50), gender (more common in males), smoking and alcohol consumption, diabetes (especially type 1 diabetes), and family history and geographic location (highest prevalence in Africa [17.2%], and the lowest prevalence in the United States [U.S.] [2.3%]).

Interventions

The therapy being considered is a local injection of clostridial collagenase.

Comparators

The following therapies and practices are currently being used to treat Dupuytren's contracture: observation and surgical therapy. 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 individuals with functional impairment and metacarpophalangeal joint contractures of 30° or more. There is no effective pharmacotherapy.

Outcomes

The general outcomes of interest are recurrence rates, improvements in functional outcomes and quality of life and treatment-related adverse events. Short-term follow-up is up to 3 days after injections are administered; long-term follow-up to monitor for recurrence is over 1 to 5 years.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.

- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Clostridial Collagenase Versus Surgery

Randomized Controlled Trials

Clostridial collagenase has been compared with percutaneous needle fasciotomy in multiple randomized controlled trials (RCTs) in individuals with Dupuytren's contracture. (7-11) All the RCTs were conducted outside of the United States. Three RCTs were single-center, 1 was a 2-center RCT, and 2 were multicenter (>2 centers) RCTs. The RCTs were heterogenous in the types of joints involved and in the definitions of treatment success and recurrence. All the trials used similar treatment protocols, and the majority of the trials explicitly included study participants with a palpable cord (Table 2). After 2 to 3 years follow-up, there were no statistically significant differences between treatment groups for any outcome measure (Table 3), suggesting that clostridial collagenase and surgery provide similar long-term benefits. In the study conducted by Dias et al. (2024) (12), collagenase was not non-inferior to surgical intervention at 1 year. It is notable that recurrence commonly occurred in both treatment groups across all studies. The studies had some methodological limitations, most notably not reporting outcome clinical significance a priori and lack of blinding (Tables 4 and 5).

The longest duration of follow-up occurred in a small, single-center, unblinded RCT in Norway (Hauksson et al. 2024). (13) Patients (N=80) were followed for up to 5 years. There was a significant improvement in contracture with collagenase compared to surgical intervention at 2 years (primary outcome), but not at 5 years (Table 3). There were no other significant differences in outcomes at 2 or 5 years between groups. The correction of contracture lasted longer in the collagenase group, although the study wasn't powered to detect this difference.

Table 2. Summary of RCT Characteristics Comparing Clostridial Collagenase to Surgery

Study	**Countries**	**Sites**	**Dates**	**Duration of follow-up**	**Participants**	**Interventions**	
						Clostridial collagenase injection	**PNF**
Dias (2024) (12) DISC trial	United Kingdom	31	2017-2021	2 years	Dupuytren's disease with a palpable cord with an extension deficit of ≥30° in a single finger	n=314 Collagenase (dose not described) injected as 3 injections; after 1 to 7 days, the cord was ruptured	n=285 Limited fasciectomy performed as day surgery; involved removal of diseased cords to

						by manipulation under local anesthetic	correct the contracture
Räisänen (2024) (14, 15) DETECT trial	Finland	6	2017-2021	2 years	Dupuytren's disease with a passive extension deficit of ≥20° in PIP or metacarpophalangeal joint; presence or absence of a palpable cord not reported	n=100 Collagenase (dose not described) injected as 1 injection up to 3 total injections; after 1 to 3 days, the cord was ruptured by manipulation under local anesthetic	n=101 Repetitive penetrations of the pathologic cord with an 18-gauge needle from a distal portal to a proximal portal, until rupture and the finger was fully extended
Hauksson (2024) (13)	Norway	1	2013-2016	5 years	Dupuytren's disease with a unilateral palpable cord metacarpo-phalangeal contracture ≥30° in a single ulnar finger	n=40 0.58 mg collagenase injected into the palpable cord in the proximal zone 2 of the involved digit, followed by an extension manipulation 1 day later under use of anesthetic	n=40 Repetitive penetrations of the palpable cord with a 26-gauge needle with continuous extension applied to the finger
Abe (2020) (7)	Japan	1	2014-2016	3 years	Dupuytren's disease of proximal interphalangeal joints with ≥30° total passive extension deficit in a single digital ray; presence or	n=36 0.58 mg (0.20 to 0.25 ml) 1 session of 3 injections, if multiple joints were affected, a second injection	n=36 Repetitive penetrations of the pathologic cord with a 25-gauge needle from a distal

					absence of a palpable cord not reported	session was scheduled for 1 month apart	portal to a proximal portal, until rupture and the finger was fully extended
Stromberg (2018) (8)	Sweden	1	2012-2014	2 years	Dupuytren's disease of the metacarpophalangeal joint with a palpable cord with an extension deficit of ≥20° in a single finger	n=78 0.58 mg (0.39 ml) injected into the pretendinous cord at the MCP level in 3 portions; following injections a forced extension maneuver was performed to disrupt the cord and, if this was unsuccessful after 3 trials, the patient was scheduled for a second treatment in 1 month	n=78 Injection of methylprednisolone and mepivacaine with a 25-gauge needle volarly and dorsally in relation to the pretendinous cord at the MCP level and, with the finger gently extended passively, the needle was passed through the cord repeatedly in various directions from the skin puncture site until the cord ruptured
Skov (2017) (9)	Denmark	1	2012-2013	2 years	Dupuytren's disease of proximal interphalangeal joints with ≤20° PIP joint passive extension deficit	n=29 0.58 mg (0.20 ml) injected into the palpable cord using a 27-gauge needle;	n=21 Repeated perforation of the cord with a 25-gauge needle while the

					and a well-defined (palpable) cord	manipulation was performed after approximately 1 day	finger was passively stretched to better visualize the cord and determine the perforation site; the finger was passively stretched to rupture the cord to complete the procedure
Scherman (2016) (10) and Scherman (2018) (11)	Sweden	2	2012-2013	3 years	Dupuytren's disease (excluding the thumb; primarily metacarpophalangeal joints) with a palpable cord, a total passive extension deficit between 30 and 135°, and a passive extension deficit ≤60° in the proximal interphalangeal joint	n=36 0.58 mg (0.20 ml) injected into the palpable cord; if needed, the joints were then manipulated up to 3 times	n=40 Contracture released under simultaneous passive extension using 19-gauge needles through 1 to 4 (mean 1.8) portals along the cord

MCP: metacarpophalangeal; PIP: proximal interphalangeal; PNF: percutaneous needle fasciotomy; RCT: randomized controlled trial.

Table 3. Summary of RCT Results Comparing Clostridial Collagenase to Surgery

Study	Treatment Success	Recurrence	Function	Major Adverse Events
Dias (2024) (12) DISC trial				

Clostridial collagenase injection	At 1 year (primary outcome): • PEM score: 17.8	17.2% by 2 years (32/186)	URAM score: data NR	2%
PNF	At 1 year (primary outcome): • PEM score: 11.9	13.5% by 2 years (22/259)	URAM score: data NR	5%
Difference (95% CI)	At 1 year (primary outcome): • 5.9 (3.1-8.8) At 2 years: • 7.2 (4.2 to 10.9)	OR: 1.39; 95% CI, 0.74 to 2.63	At 1 year: • 3.42 (2.18 to 4.66)	RR, 0.4; 95% CI, 0.1 to 0.9
p-value	At 1 year: • p=.49 (NI)[a] At 2 years: • NR	-	-	NR
Räisänen (2024) (14, 15) DETECT trial				
Clostridial collagenase injection	At 3 months: • 73% (70/100) At 2 years: • 65% (59/92)	NR	NR	0% (0/100)
PNF	At 3 months: • 74% (68/96) At 2 years: • 50% (46/95)	NR	NR	1% (1/101)
Difference (95% CI)	At 3 months: • 0.00 (-0.12 to 0.12) At 2 years: • -0.17 (-0.30 to -0.03)	NR	NR	-
Hauksson (2024) (13)				
Clostridial collagenase injection	Mean improvement in MCP contracture (SD): At 2 years: -4° (16.3°) At 5 years: 2° (23.6°)	At 2 years: • MCP: 0% (0/40) • PIP: 15% (6/40) • Total: 15% (6/40) At 5 years: • MCP: 12.5% (5/40) • PIP: 27.5% (11/40) • Total: 40% (16/40)	Mean URAM score (SD): At 2 years: 2 (3.6) At 5 years: 6 (9.2)	Total adverse reactions at 4 weeks: 20% (8/40)
PNF	Mean improvement in MCP contracture (SD): At 2 years: 9° (21.0°) At 5 years: 7° (23.0°)	At 2 years: • MCP: 25% (10/40) • PIP: 22.5% (9/40) • Total: 47.5% (19/40) At 5 years:	Mean URAM score (SD): At 2 years: 3 (4.6)	Total adverse reactions at 4 weeks:

		• MCP: 32.5% (13/40) • PIP: 32.5% (13/40) • Total: 65% (26/40)	At 5 years: 4(5.8)	12.5% (5/40)
Difference (95% CI)	At 2 years: 13.4° (6.2°to 20.6°) At 5 years: 5.7° (-1.5°to 12.8°)	-	At 2 years: 0.7 (-1.6 to 3.1) At 5 years: -1.8 (-4.2 to 0.5)	-
p-value	At 2 years: p<.001 At 5 years: p=.1	-	At 2 years: p=.5 At 5 years: p=.1	-
Abe (2020) (7)				
Clostridial collagenase injection	At 30-days: • MCP joint: 100% • PIP joint, Stage 1: 89% • PIP joint, Stage 2: 50%	• MCP joint: 26% (8/31) • PIP joint, Stage 1: 44% (4/9) • PIP joint, Stage 2: 67% (4/6)	URAM score: 2.9	0% (0/36)
PNF	At 30-days: • MCP joint: 100% • PIP joint, Stage 1: 100% • PIP joint, Stage 2: 67%	• MCP joint: 29% (9/31) • PIP joint, Stage 1: 38% (3/8) • PIP joint, Stage 2: 67% (6/9)	URAM score: 3.9	5.9% (2/34)
p-value	• MCP joint: p=NR • PIP joint, Stage 1: p=NR • PIP joint, Stage 2: p=NR	• MCP joint: p>.05 • PIP joint, Stage 1: p>.05 • PIP joint, Stage 2: p>.05	p>.05	p>.05
Stromberg (2018) (8)				
Clostridial collagenase injection	76% (58/76)	13% (10/76)	URAM score: data NR	NR
PNF	79% (60/76)	12% (9/76)	URAM: data NR	NR
p-value	p=.697	p=.806	p=.570	NR
Skov (2017) (9)				
Clostridial collagenase injection	Clinical improvement (≥50% reduction in contracture): 7% (2/29)	83% (24/29)	NR	3% (1/29)

PNF	Clinical improvement (≥50% reduction in contracture): 29% (6/21)	68% (14/21)	NR	0% (0/21)
p-value	p=.05	p=.25	NR	p=.62
Scherman (2018) (11)				
Clostridial collagenase injection	Retreatment rate: 11% (4/35)	33% (12/36)	URAM: 3 (IQR 8)	NR
PNF	Retreatment rate: 24% (11/45)	43% (17/40)	URAM: 1 (IQR 5)	NR
p-value	p=.09	p=.65	p>.05	NR

CI: confidence interval; IQR: Interquartile range; MCP: metacarpophalangeal; NI: non-inferiority; NR: Not Reported; OR: odds ratio; PEM: Patient Evaluation Measure Hand Health Questionnaire; PIP: proximal interphalangeal; PNF: percutaneous needle fasciotomy; RCT: randomized controlled trial; RR: risk ratio; SD: standard deviation; URAM: Unité Rhumatologique des Affections de la Main scale (a measure of hand function); °: degrees.

[a] Collagenase was not non-inferior to limited fasciectomy (NI margin for PEM at 1 year was +6 points.)

Table 4. Study Relevance Limitations in RCTs Comparing Clostridial Collagenase to Surgery

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-up[e]
Dias (2024) (12); DISC trial	4. Predominately white population				1,2. Due to pandemic related delays, 31% of participants did not complete 2 year FU; longer FU needed to better assess progression of contracture and re-intervention rates
Räisänen (2024) (14,15); DETECT trial					1,2. longer FU needed to better assess benefits and harms

Hauksson (2024) (13)	5. Small sample size at single center				
Abe (2020) (7)	3. Presence or absence of palpable cord not reported			5	
Stromberg (2018) (8)				3	
Skov (2017) (8)					
Scherman (2016) (10) and Scherman (2018) (11)				5	

FU: follow-up; RCT: randomized controlled trial.

The evidence limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.

[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest.

[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.

[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.

[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 5. Study Design and Conduct Limitations in RCTs Comparing Clostridial Collagenase to Surgery

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Dias (2024) (12); DISC trial		1, 2				
Räisänen (2024) (14, 15); DETECT trial		1, 2				

Hauksson (2024) (13)		1, 2				
Abe (2020) (7)		1, 2	1		1	3; only p-values reported
Stromberg (2018) (8)		1				3; only p-values reported
Skov (2017) (9)		1, 2				
Scherman (2016) (10) and Scherman (2018) (11)	3	2, 3	1			3; only p-values reported

RCT: randomized controlled trial.
The evidence limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.
[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.
[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

Nonrandomized Studies

Clostridial collagenase has been compared to surgery other than percutaneous needle fasciotomy in 3 small, mostly short-term nonrandomized studies (N=132) (Table 6). (16-18) Compared with surgery, findings from these studies suggest that clostridial collagenase may provide similar benefits and fewer adverse events at least in the short-term. However, their small sample sizes, lack of long-term follow-up, and limited data on the most clinically meaningful outcomes preclude reaching strong conclusions based on their findings.

Table 6. Summary of Nonrandomized Studies Comparing Collagenase Clostridium to Surgery

Study	Study Type	Country	Surgical Comparator	Follow-Up	N	Success	Major adverse events	Recurrence
Zhou (2015) (16)	Cohort	The Netherlands (7 sites)	Limited fasciectomy	3 months	66	NR	0% versus 6%	NR
Povlsen (2014) (17)	Prospective	United Kingdom (1 site)	Open fasciectomy	3 to 5 days	20	NR	NR	NR
Naam (2013) (18)	Retrospective	USA (1 site)	Fasciectomy	32 months	46	NR	NR	None

NR; not reported; USA: United States of America.

Clostridial Collagenase Versus Placebo

Systematic Reviews

In individuals with Dupuytren's contracture, for the comparison of collagenase injection to placebo and for long-term outcomes, the best available evidence comes from systematic reviews by Smeraglia et al. (2016) (19) and Brazzelli et al. (2015) (20) (Table 7). The review by Smeraglia et al. (2016) includes the largest number of studies to-date, but it did not include any quantitative analyses. Therefore, quantitative findings from the next largest and most recent review by Brazzelli et al. (2015) are also provided (Table 8). Both reviews included the 3 placebo-controlled RCTs (21-23) sponsored by Xiaflex manufacturer Auxilium Pharmaceuticals. The reviews also included numerous nonrandomized comparative studies (18, 24) and noncomparative studies (25-31) to address gaps in the RCTs for recurrence rates.

Table 7. Key Systematic Reviews & Meta-Analyses Characteristics

Study	Dates	Studies	Participants	N (Range)	Design	Duration
Smeraglia (2016) (19)	2000-2015	43	Dupuytren's contracture	6795 (4 to 715)	9 RCTs; 10 nonrandomized comparative studies; 24 case series and cost analyses	Mean follow-up=15 months (range, 1 to 96 months)
Brazzelli et al. (2015) (20)	2000-2014	23[a]	Dupuytren's contracture	3737 (8 to 643)	5 RCTs; 2 non-randomized comparative studies; 16 case series	Range, 4 weeks to 8 years

[a] The health technology assessment by Brazzelli et al. (2015) included studies that focused only on comparing different surgical interventions and did not include a collagenase arm. Those studies that did not include a collagenase arm were not included in the counts of numbers of studies, sample sizes and duration as they do not provide information about collagenase.

RCT: randomized controlled trial.

The reviews rated the RCTs as having low risk of important biases. Limitations included lack of blinding of outcome assessors. The RCTs were also industry sponsored. The Dupuytren's contracture selection criteria used in the RCTs included that participants have 1 cord, contracture between 20° and 100° for the metacarpophalangeal joint, and contracture between 20° and 80° for the proximal interphalangeal joint. Mean baseline contracture for the metacarpophalangeal and proximal interphalangeal joints ranged from 44° to 51° and from 43° to 53°, respectively.

In the RCTs, the clinically meaningful outcome was 'clinical success', which was defined as a reduction in contracture to 0 to 5 degrees of normal, within 30 days after the last injection. Pooled analyses from the review by Brazzelli et al. (2015) found greater rates of clinical success for clostridial collagenase (63%; range 44% to 91%) compared with placebo (6%; range 0% to 7%), which was a statistically significant difference (Table 8). The clinical success advantage for clostridial collagenase compared to placebo was greater for the metacarpophalangeal joints (relative risk [RR], 10.27; 95% confidence intervals [CI], 4.88 to 21.65; n=254) compared to the proximal interphalangeal joints (RR, 7.44; 95% CI, 2.44 to 22.62; n=153)

Adverse events were significantly more frequent for participants receiving clostridial collagenase compared with placebo. In the RCTs, the proportions of participants experiencing at least 1 adverse event were 97% in the clostridial collagenase groups (range, 97% to 100%) and 28% in the placebo groups (range, 21% to 75%). Peripheral edema was the most frequent adverse event reported, which occurred in 73% of participants receiving clostridial collagenase compared with 5% in the placebo groups. The next most common mild and local adverse events included contusion, pain in extremity, and injection site pain. Serious adverse events were rare and not evaluated in a meta-analysis. Only 1.5% of participants who received clostridial collagenase (4/272) experienced a serious adverse event, including 1 case of complex regional pain syndrome and 2 cases of tendon rupture in CORD I and 1 case of flexion pulley rupture in CORD II.

Table 8. Key Results of Brazzelli et al. (2015) Systematic Review and Meta-Analysis

Study	Clinical Success (Residual Contracture < 5°)	≥ 1 adverse event	peripheral edema	Contusion	Pain in extremity	Injection site pain
Brazzelli et al. (2015) (20)						
# RCTs; Total N	3; 407	3; 409	2; 374	2; 374	2; 374	3; 409
Range of N	25 to 306	35 to 308	66 to 308	66 to 308	66 to 308	35 to 308
Range of effect sizes: RR (95% CI)	9.33 (1.34, 64.98) to 23.29 (1.53, 354.07)	1.34 (0.96, 1.87) to 4.57	8.17 (2.17, 30.80) to 18.86	7.70 (2.04, 29.11) to 26.51	5.13 (1.33, 19.83) to 5.13 (1.33, 19.83)	1.96 (1.13, 3.38) to 6.73 (2.80, 16.19)

		(3.15, 6.62)	(7.19, 49.49)	(6.68, 105.28)		
Pooled effect (95% CI)	RR 10.21 (5.29, 19.69)	RR 2.49 (1.13, 5.50)	RR 15.23 (6.97, 33.29)	RR 14.09 (4.20, 47.30)	RR 6.26 (3.00, 13.09)	RR 3.49 (1.48, 8.27)
I^2	0%	91%	3%	37%	0%	65%

CI: confidence interval; RR: Relative Risk; RCT: randomized controlled trial.

In the systematic review by Smeraglia et al. (2016), recurrence was typically defined as a decrease in passive extension that exceeded 20 degrees and was reported in 12 studies (N=2401) (Table 9). This included data from the RCTs with follow-up that ranged from 3 to 24 months, (21-23) as well as from an additional 9 nonrandomized studies with follow-up that extended to 88 months. (18, 24-31) Neither review performed meta-analyses on this outcome, but both reviews observed that recurrence rates tended to increase over time. Recurrence rates ranged from 0% to 4% in studies with follow-up from 3 to 12 months, from 0% to 28% in studies with follow-up of 15 to 24 months, and from 36% to 75% in studies with follow-up from 36 to 88 months. However, authors of the review by Smeraglia et al. (2016) (19) and the nonrandomized, surgery-controlled study by Nydick et al. (2013) (24) have raised questions about the clinical relevance of defining recurrence as a decrease in passive extension that exceeded 20 degrees. For example, authors of Nydick et al. (2013) (24) pointed out that although the recurrence rate of 75% is high in the longest-term, a very small case series by Watt et al. (2010) noted, "none of these patients had further intervention on the injected finger." Further, authors of the review by Smeraglia et al. (2016) (19) proposed that a more clinically relevant definition of recurrence may be contracture greater than 30 degrees, as this is the threshold for which surgery is indicated. In the Collagenase Option for Reduction of Dupuytren Long-Term Evaluation of Safety Study (CORDLESS) study, using the threshold of contracture greater than 30 degrees led to a lower rate of 5-year recurrence of 32%. (26)

Table 9. Summary of Recurrence Results from the Smeraglia 2016 Review According to Duration of Follow-up (19)

Study	Design	Setting	N enrolled	Months of Follow-Up	Recurrence
Hurst (2009) CORD (22)	RCT	USA (16 sites)	306	3	0/306 (0%)
Nydick (2013) (24)	Nonrandomized comparative study	USA (1 site)	59	6	0/59 (0%)
Alberton (2014) (27)	Case series	Italy (1 site)	40	6	2/40 (3.8%)
Witthaut (2013) JOINT I/II (28)	Case series	USA, Australia, UK, Switzerland,	587	9	19/497 (4%)

		Sweden, Denmark, Finland (34 sites)			
Gilpin (2010) CORD II (21)	RCT	Australia (5 sites)	66	12	0/66 (0%)
McMahon (2013) (29)	Case series	USA (1 site)	48	15	13/48 (28%)
Badalamene (2000) (30)	Case series	USA (sites NR)	35	20	3/35 (8.5%)
Naam (2013) (18)	Nonrandomized comparative study	USA (1 site)	46	24	0/46 (0%)
Badalamene (2007) (23)	RCT	USA (sites NR)	35	24	5/35 (14%)
Peimer (2013) CORDLESS (25)	Case series	USA (10 sites)	643	36	217/623 (35%)
Peimer (2015) CORDLESS (26)	Case series	USA (10 sites)	643	60	291/623 (47%)
Watt (2010) (31)	Case series	USA (1 site)	8	88	6/8 (75%)

CORD: Collagenase Option for Reduction of Dupuytren; CORDLESS: Collagenase Option for Reduction of Dupuytren Long-Term Evaluation of Safety Study; JOINT I: clinicaltrials.gov title: "A Phase 3, Open-Label Study of the Safety and Efficacy of AA4500 in the Treatment of Subjects With Advanced Dupuytren's Disease"; JOINT II: Australian New Zealand Clinical Trials Registry Name, "An Open-Label Study of the Safety and Efficacy of AA4500 in the Treatment of Subjects With Dupuytren's Contracture"; RCT; randomized controlled trial; USA: United States of America; UK: United Kingdom; NR: Not Reported.

For functional outcomes, relevant findings were identified from only 1 open-label, single-arm study (JOINT I, acronym definition not found, clinicaltrials.gov title - "A Phase 3, Open-Label Study of the Safety and Efficacy of AA4500 in the Treatment of Subjects With Advanced Dupuytren's Disease") reported by Naam et al. (2013). (18) This study retrospectively assessed patients who had Dupuytren's contracture affecting at least 1 joint with a palpable cord who underwent clostridial collagenase injections (n=25) or fasciectomy (n=21). Over an average follow-up of 32 months for patients treated with clostridial collagenase and 39 months for those treated with fasciectomy, mean posttreatment contracture, decrease in contracture from baseline, and increase in range of motion from baseline at the metacarpophalangeal and proximal interphalangeal joints did not differ significantly. Mean posttreatment range of motion at the metacarpophalangeal joint was significantly higher in the clostridial collagenase-treated patients (90.7° versus 83.3°, p=.02), while the posttreatment range of motion at the proximal interphalangeal joint was higher in the fasciectomy-treated patients, although the difference was not statistically significant (67.5° versus 88.8°, p=.06). Complication rates were similar in both groups, although patients who received clostridial collagenase returned more quickly to work and to normal daily activities.

No study has yet reported any quality of life outcomes.

Section Summary: Dupuytren's Contracture

For individuals with Dupuytren's contracture who receive clostridial collagenase, the evidence includes systematic reviews, randomized controlled trials, and nonrandomized comparative studies. Relevant outcomes are symptoms, change in disease status, functional outcomes, and quality of life. Findings from randomized and nonrandomized studies comparing clostridial collagenase to surgery suggest similar benefits and harms. However, limited data on the most clinically meaningful outcomes preclude reaching strong conclusions based on their findings. Findings from systematic reviews of randomized, placebo-controlled trials, nonrandomized controlled studies, and noncomparative studies consistently demonstrated clinically important benefits for clostridial collagenase. However, data on quality of life have not yet emerged. Rates of mild local adverse events, including local swelling, contusion, and pain, are generally high, but serious adverse events have been rare. In comparative studies, the risk of contracture recurrence appears to increase over time regardless of treatment group. However, as recurrence rates vary by the definition of recurrence (contracture greater than 20°, or 30°, and/or when further intervention is needed), standardization of definition is still needed. Although clostridial collagenase offers the potential benefit of less-invasive treatment for Dupuytren's contracture with clinically meaningful benefits and a low risk of major complications, important gaps in the evidence base exist related to treatment durability and impact on quality of life.

Peyronie's Disease

Clinical Context and Therapy Purpose

The purpose of administering local clostridial collagenase injection(s) in individuals who have Peyronie's disease is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this policy.

Populations

The relevant population of interest is individuals with Peyronie's disease. 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 3% to 9% of men, most commonly between the ages of 45 and 60 years. 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.

Interventions

The therapy being considered is a local injection of clostridial collagenase.

Comparators

The following therapies and practices are currently being used to treat Peyronie's disease: observation, oral medications, and other intralesional treatment (e.g., verapamil). The goal of treatment is to reduce pain and maintain sexual function. Treatments in early stages (before

calcification) include vitamin E or para-aminobenzoate tablets (e.g., Potaba®), although studies of oral therapies have demonstrated inconsistent benefit. Intralesional injection therapy consisting of interferon-α-2b or calcium channel-blockers (e.g., verapamil) is the current standard of therapy. (32) Surgical procedures involve the excision of hardened tissue and skin graft, the removal or pinching (plication) of tissue opposite the plaque to reduce curvature (the Nesbit procedure), penile implant, or a combination of these.

Outcomes

The general outcomes of interest are improvements in functional outcomes and quality of life (e.g., sexual function) and treatment-related adverse events (e.g., rupture, hematoma).

Injections are administered 1- to 3-day cycles at specific intervals over about 24 weeks depending on the degree of curvature, followed by manual modeling.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Systematic Reviews

Cao et al. (2022) (33) conducted a systematic review and meta-analysis of 5 RCTs comparing clostridial collagenase with placebo, including the Investigation for Maximal Peyronie's Reduction Efficacy and Safety Studies (IMPRESS) I and II studies (34), described below in the RCT section. The review included evidence from 1227 individuals (mean age, 57 years), including 815 who received clostridial collagenase and 412 who received placebo. Pooled results favored clostridial collagenase over placebo for penile curvature deformity (weighted mean difference [WMD], -18.77; 95% CI, -22.58 to -14.96; I^2=38%) and Peyronie's Disease Symptom Bother (WMD, -1.20; 95% CI, -1.69 to -0.72; I^2=0%). The review found no statistically significant difference between clostridial collagenase and placebo (WMD, -0.64; 95% CI, -2.09 to 0.81) and heterogeneity was high (I^2=67%). Treatment-related adverse events were more likely to occur with clostridial collagenase compared with placebo (OR, 12.86; 95% CI, 9.17 to 18.04; I^2=0%). Specific event rates were also higher with clostridial collagenase than placebo, including penile pain (odds ratio [OR], 8.87; 95% CI, 5.43 to 14.50; I^2=0%), edema (OR, 26.86; 95% CI, 6.63 to 108.0; I^2=0%), injection site pain (OR, 7.91; 95% CI, 4.38 to 14.30; I^2=0%), and contusion (OR, 14.60; 95% CI, 4.13 to 51.68; I^2=0%) based on imprecise risk estimates. Study authors noted that while these results appear promising, confirmatory RCT evidence with larger sample sizes is needed.

A 2023 Cochrane review of non-surgical therapies for Peyronie's Disease included only one publication (Gelbard et al. [2013]), which is summarized below, for outcomes associated with collagenase injections in this population. (35)

Randomized Controlled Trials

Gelbard et al. (2013) published the results of 2 double-blind, placebo-controlled randomized trials, the Investigation for Maximal Peyronie's Reduction Efficacy and Safety Studies (IMPRESS) I and II, which examined the clinical efficacy and safety of collagenase injections in subjects with Peyronie's disease. (34) These RCTs were sponsored by the manufacturer (Auxilium Pharmaceuticals), the findings of which were submitted to the U. S. Food and Drug Administration in support of their biologics license application. These 2 trials examined collagenase injections in 417 and 415 participants, respectively, through a maximum of 4 treatment cycles, each separated by 6 weeks (for up to 8 injections of collagenase). Men were stratified by baseline penile curvature (30° to 60° versus 61° to 90°) and randomized to collagenase injections or placebo in a 2:1 ratio. The primary outcomes were the percent change in the penile curvature abnormality as well as the change in the Peyronie's Disease Questionnaire (PDQ; developed by the manufacturer; see discussion at the end of this section on PDQ validation) symptoms bother score from baseline to 52 weeks. Data from the IMPRESS I and II studies were pooled. Participants treated with collagenase injections showed a mean percent improvement in penile curvature abnormality of 34% compared with 18% improvement in penile curvature in the placebo group. The change in curvature and the percent improvement in the collagenase group were significantly greater in the injection group (each p<.001). The mean change in the PDQ symptom bother domain score was significantly improved in the collagenase group (-2.8) compared with the placebo group (-1.8; p=.004). The most frequently reported complications (≥45%) in the collagenase-treated group included penile ecchymosis, penile swelling, and penile pain. Six participants experienced treatment-related serious adverse events, including corporeal rupture (3 cases) and penile hematoma (3 cases). All corporeal ruptures and 1 hematoma were successfully repaired surgically. Of the other 2 penile hematomas, 1 case resolved successfully without intervention and the other ended with aspiration.

Lipshultz et al. (2015) reported post hoc subgroup analyses from combined data from the IMPRESS I and II studies. (36) This analysis included a modified intention-to-treat population of 612 subjects who had a penile curvature deformity measurement, a PDQ response at baseline and at least 1 subsequent time point after the first injection of clostridial collagenase. Subgroups included those stratified based on the duration of illness, the degree of plaque calcification, and the International Index of Erectile Function (IIEF) severity score. Reductions in penile curvature deformity occurred in all groups, though the reductions were significantly greater with clostridial collagenase than with placebo for those with baseline penile curvature 30° to 60° and 61° to 90°, disease duration over 2 years, no calcification, and IIEF severity score of 17 or greater. PDQ symptom bother score reductions were significantly greater with clostridial collagenase than with placebo for those with penile curvature 30° to 60°, disease duration over 4 years, no calcification, and IIEF scores 1 to 5 (no sexual activity) and 17 or

greater. However, a generalization of this analysis is limited by its post hoc design and small subgroups.

The development and validation of the PDQ have been described by Hellstrom et al. (2013) using data from IMPRESS I and II studies. (37) Investigators developed the PDQ to assess quantitatively the symptoms and psychosexual consequences of Peyronie's disease by 3 subscale domain scores, including psychological and physical symptoms (6 items), penile pain (3 items), and symptom bother (4 scored items and 2 yes/no questions). Questions were evaluated using baseline data for 679 (81% of the total 836 enrolled) patients in IMPRESS I and II who had been sexually active in the last 3 months. PDQ domain scores did not significantly differentiate between patients with different degrees of curvature abnormality. Coyne et al. (2015) assessed the responsiveness of the PDQ to changes in Peyronie's disease symptoms in men from the IMPRESS I and II trials. (38) In this group, PDQ psychological and physical symptoms and symptom bother subscales significantly discriminated patient improvement in responses to a global assessment of the PDQ and degree of penile curvature at weeks 24 and 52.

Noncomparative Studies

Case series have reported Peyronie's disease outcomes after treatment with clostridial collagenase. Many series are small (e.g., ~20 patients) (39) or from earlier treatment eras (e.g., 1985), which limit their utility. However, some larger studies provide data on adverse events after clostridial collagenase treatment for Peyronie's disease.

Goldstein et al. (2020) reported noncomparative 5-year outcomes in men treated with clostridial collagenase. (40) The study included 280 men previously enrolled in the IMPRESS I and II trials or in the AUX-CC 802 or 806 open-label studies. After a mean 4.6 years follow-up, in 180 men with data, there was a 9.1% improvement in mean penile curvature relative to their final measure in their original study enrollment. Mean PDQ bother (N=123; p=.0003), psychological and physical symptoms (N=119; p=.0004), and pain (N=52; p=.04) were all significantly improved compared with the last measure of their previous study. Serious adverse events occurred in 2.1% (6/280) of the population. Due to the high number of participants with missing follow-up data (27%) and the lack of a comparison group, these study results should be interpreted with caution.

A single-arm, open-label trial reported by Levine et al. (2015) described outcomes for 238 subjects with Peyronie's disease treated with clostridial collagenase who had both a penile curvature measurement and a PDQ response at baseline and at least 1 subsequent time point (of 347 total subjects treated). (41) The degree of penile curvature improved from baseline to week 36 (34.4%; 95% CI, 31.2% to 37.6%) as did PDQ symptom bother score (mean change, 3.3; 95% CI, 2.8 to 3.7). However, the lack of a comparison group and exclusion of a high proportion of subjects (missing follow-up data) limit conclusions that can be drawn.

Section Summary: Peyronie's Disease

The most direct evidence on the use of clostridial collagenase injections to treat Peyronie's disease comes from 2 industry-sponsored RCTs that compared clostridial collagenase with placebo. Clostridial collagenase-treated subjects demonstrated significant improvements in penile curvature (absolute percentage improvement, 16%) and reported improvements in their degree of bothersomeness related to the disease. However, it is not clear that these improvements in curvature or in the degree of symptom bothersomeness translate into differences in patient outcomes or whether the benefit of treatment exceeds the risks.

Although important uncertainties remain in the peer-reviewed scientific literature that preclude definitely determining whether the technology improves the net health outcome, the 2010 FDA approval and the American Urological Association's 2015 guidelines support use of intralesional collagenase Clostridium histolyticum in combination with modeling in patients with stable Peyronie's disease, penile curvature greater than 30° and less than 90°, and intact erectile function.

Adhesive Capsulitis

Clinical Context and Therapy Purpose

The purpose of administering local clostridial collagenase injection(s) in individuals who have adhesive capsulitis is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this policy.

Populations

The relevant population of interest is individuals with adhesive capsulitis, which is also commonly referred to as 'frozen shoulder'.

Interventions

The therapy being considered is a local injection of clostridial collagenase.

Comparators

The following therapies and practices are currently being used to treat adhesive capsulitis: physical therapy and mobilization in combination with analgesics or nonsteroidal anti-inflammatory drugs.

Outcomes

The general outcomes of interest are improvements in symptom improvement, functional outcomes, quality of life, and treatment-related adverse events.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.

- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Evidence on the use of clostridial collagenase for treatment of adhesive capsulitis is extremely limited. Fitzpatrick et al. (2020) (42) reported results from 11 participants enrolled at a single center comparing clostridial collagenase injection (n=9) with placebo (n=2). There was no statistically significant difference between clostridial collagenase and placebo in shoulder function based on measures of range of motion after 3 months of follow up. Adverse events that included bruising and swelling occurred in 100% (9/9) of participants receiving clostridial collagenase injection and no (0/2) placebo participants. These results are part of a larger randomized trial of 322 participants at 46 sites which was completed in 2014 (NCT02006719). Complete results for the trial remain unpublished although Fitzpatrick et al. note that their findings were consistent with those of the full trial population.

Section Summary: Adhesive Capsulitis

Evidence on the use of clostridial collagenase for treatment of adhesive capsulitis is extremely limited. One small substudy of a larger, unpublished RCT found no benefit of clostridial collagenase injection over placebo in functional outcomes, with increased adverse events.

Summary of Evidence

For individuals with Dupuytren's contracture who receive clostridial collagenase, the evidence includes systematic reviews, randomized controlled trials, and nonrandomized comparative studies. Relevant outcomes are symptoms, change in disease status, functional outcomes, and quality of life. Findings from randomized and nonrandomized studies comparing clostridial collagenase to surgery suggest similar benefits and harms. However, limited data on the most clinically meaningful outcomes preclude reaching strong conclusions based on their findings. Findings from systematic reviews of randomized, placebo-controlled trials, nonrandomized controlled studies, and noncomparative studies consistently demonstrated clinically important benefits for clostridial collagenase. However, data on quality of life has not yet emerged. Rates of mild local adverse events, including local swelling, contusion, and pain, are generally high, but serious adverse events have been rare. In comparative studies, the risk of contracture recurrence appears to increase over time regardless of treatment group. However, as recurrence rates vary by the definition of recurrence (contracture greater than 20 degrees, or 30 degrees, and/or when further intervention is needed), standardization of the definition is still needed. Although clostridial collagenase offers the potential benefit of less-invasive treatment for Dupuytren's contracture with clinically meaningful benefits and a low risk of major complications, important gaps in the evidence base exist related to treatment durability and impact on quality of life. The U.S. Food and Drug Administration (FDA) approved clostridial collagenase for adults with Dupuytren's contracture with a palpable cord and up to 3 injections at 4-week intervals into a palpable Dupuytren's cord with a contracture of a

metacarpophalangeal or a proximal interphalangeal joint. Therefore, this treatment is deemed medically necessary when criteria are met.

For individuals who have Peyronie's disease who receive local clostridial collagenase injection(s), the evidence includes a systematic review, randomized trials and numerous noncomparative comparative studies. Relevant outcomes are symptoms, change in disease status, functional outcomes, and quality of life. The available double-blind, placebo-controlled randomized trials have demonstrated short-term improvement in penile curvature and reductions in self-reported distress from symptoms related to Peyronie's disease. The FDA approved clostridial collagenase for the treatment of Peyronie's disease in men with a palpable penile plaque and penile curvature >30 degrees and a maximum of 4 cycles, each of which consists of 2 Xiaflex injection procedures. Therefore, this treatment is deemed medically necessary when criteria are met.

For individuals who have adhesive capsulitis who receive local clostridial collagenase injection(s), evidence is lacking. Relevant outcomes are symptoms, change in disease status, functional outcomes, and quality of life. One small substudy of an RCT found no benefit of clostridial collagenase injection over placebo in functional outcomes, with increased adverse events. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Practice Guidelines and Position Statements

Peyronie's Disease

American Urological Association (AUA)

In 2015, the AUA issued guidelines based on a systematic review on the diagnosis and treatment of Peyronie's disease. (5) For patients with stable Peyronie's disease, penile curvature greater than 30° and less than 90°, and intact erectile function (with or without the use of medications), the AUA recommended intralesional collagenase *Clostridium histolyticum* in combination with modeling (Moderate recommendation; evidence Strength Grade B). The AUA panel discussion indicated that their recommendation was based primarily on the IMPRESS I and II RCTs discussed above. They acknowledge that some uncertainty remains about the long-term durability of curvature improvements, replication by another group of investigators, and generalizability to other patient subgroups such as those with hourglass deformity, ventral curvature, calcified plaque, or plaque located proximal to the base of the penis. Ultimately, their moderate recommendation for clostridial collagenase was because of the modest curvature reductions obtained and the low risk of serious adverse events in IMPRESS I and II.

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this policy are listed in Table 10.

Table 10. Summary of Key Trials

NCT Number	Trial Name	Planned Enrollment	Completion Date

Ongoing			
NCT03406338	Surgical Fasciectomy Versus Collagenase Injection in Treating Recurrent Dupuytren Disease: A Randomized Controlled Trial	60	Sept 2027
NCT04786106[a]	Comparison of Collagenase Clostridium Histolyticum to Surgery for the Management of Peyronie's Disease: A Randomized Trial	40	Feb 2027
NCT03192020	DupuytrEn Treatment EffeCtiveness Trial (DETECT): Prospective, Randomised, Controlled, Outcome Assessor-blinded, Three-armed Parallel 1:1:1, Multicenter Trial Comparing the Effectiveness and Cost of Collagenase Clostridium Histolyticum, Percutaneous Needle Fasciotomy and Limited Fasciectomy as Short-term and Long-term Treatment Strategies in Dupuytren's Contracture	302	May 2031
Unpublished			
NCT03000114	Comparison of Collagenase Injection and Percutaneous Needle Aponeurotomy for Treatment of Dupuytren's Disease	334	Jan 2021 (status: unknown)
NCT02725528	A Multi-Center, Randomized Controlled Trial Comparing The Clinical Effectiveness of Collagenase Injection (Xiaflex) and Palmar Fasciectomy in the Management of Dupuytren's Disease	128	Dec 2021 (status: completed)
NCT02301078	Comparing Short-term Function and Pain After Treatment With Collagenase Clostridium Histolyticum or Percutaneous Needle Aponeurotomy for Dupuytren's Disease	60	Nov 2017 (status: unknown)
NCT02006719[a]	A Randomized, Double-blind, Placebo-controlled Study of the Safety and Efficacy of AA4500 for the Treatment of Adhesive Capsulitis of the Shoulder	322	Dec 2014 (status: completed)[b]

NCT: national clinical trial.

[a] Denotes industry-sponsored or cosponsored trial.

[b] Results from one center (of 46) reported in Fitzpatrick et al. (2020).

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	20527, 20550, 20551, 26341, 54200, 54205, 54235
HCPCS Codes	J0775, J3590

*Current Procedural Terminology (CPT®) ©2024 American Medical Association: Chicago, IL.

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Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <https://www.cms.hhs.gov>.

Policy History/Revision

Date	Description of Change
11/15/2025	Document updated with literature review. The following change was made to Coverage: Added “(1 to 3 days after injection) to #3 “Treatment will be administered in conjunction with a penile modeling procedure” under “Injectable clostridial collagenase may be considered medically necessary for the treatment of adult individuals with Peyronie’s disease.” References 6, 12-15, 35 added; some updated. Title changed from Clostridial Collagenase for Fibroproliferative Disorders.
12/15/2024	Reviewed. No changes.
09/15/2023	Document updated with literature review. Coverage unchanged. References 28 and 36 added; some updated and others removed.
08/15/2022	Reviewed. The following change was made to Coverage: Removed information on REMS from medical necessity criteria and added as a NOTE. No new references added.
01/01/2022	Document updated with literature review. Coverage unchanged. References 2, 6-10, 19, 25, and 37 added; some updated and others removed.
04/01/2020	Document updated with literature review. Coverage unchanged. References 3 and 40 added.
04/15/2018	Reviewed. No changes.
07/15/2017	Document updated with literature review. The following editorial change was made to coverage: adhesive capsulitis was added to the EIU coverage statement.

03/15/2016	Reviewed. No changes.
08/01/2015	Document updated with literature review. The following was added to Coverage for the treatment of Dupuytren's contracture: 1) A contracture of a metacarpophalangeal (MP) joint or a proximal interphalangeal (PIP) joint. 2) A note was added to describe the FDA approved treatment course to include a) Treatment of up to 2 cords or 2 joints in the same hand may be allowed at a treatment visit. b) If a patient has more than 2 cords in the same hand, inject those cords at another visit. c) A finger extension procedure may be performed approximately 24 to 72 hours following an injection. d) Injection and finger extension procedures may be administered up to 3 times per cord at approximately 4-week intervals.
08/01/2014	Document updated with literature review. The following was added to coverage: Injectable clostridial collagenase may be considered medically necessary in adult patients with a diagnosis of Peyronie's disease when ALL of the following criteria is met: 1) Palpable plaque; and 2) Objective documentation in the medical record of a penile curvature deformity of at least 30 degrees at start of therapy, as measured using intracavernosal injection (ICI) and goniometer; and 3) Treatment will be used in combination with penile modeling procedure; and 5) 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 Clostridial Collagenase injection procedures and 1 penile modeling procedure. Injectable clostridial collagenase is considered experimental, investigational and/or unproven for all other indications.
07/15/2012	Document updated with literature review. Coverage unchanged.
12/15/2010	New medical document. Injectable Clostridial collagenase may be considered medically necessary for treatment of adult patients with Dupuytren's contracture with a palpable cord. Injectable Clostridial collagenase is considered experimental, investigational and unproven for all other indications including, but not limited to, Peyronie's disease and adhesive capsulitis.