

Collagenase Clostridium Histolyticum (XIAFLEX™) for Dupuytren's Contracture**National PBM Drug Monograph**

**VA Pharmacy Benefits Management Services,
Medical Advisory Panel, and VISN Pharmacist Executives**

The purpose of VACO PBM-SHG drug monographs is to provide a comprehensive drug review for making formulary decisions. These documents will be updated when new data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

Executive Summary

- Dupuytren's Disease is a progressive disorder of pathologic collagen production and deposition which can lead to the formation of collagen cords that thicken and shorten leading to flexion contractures that typically affect the metacarpophalangeal (MP) joint, proximal interphalangeal (PIP) joint, or both.
- Collagenase Clostridium Histolyticum (CCH) hydrolyzes collagen resulting in lysis of collagen deposits and may result in enzymatic disruption of the cord. It is FDA approved for treatment of adult patients with Dupuytren's contracture with a **palpable cord**.
- The dose is 0.58 mg per injection into a palpable cord with a contracture of a MP joint or PIP joint. If contracture remains 4 weeks after the injection and finger extension procedure, the cord may be re-injected with a single 0.58mg dose with repeat finger extension procedures. Injections and finger extension procedures may be administered up to 3 times per cord at approximately 4-week intervals.
- Up to 2 cords may be treated in the same hand at a treatment visit (2 palpable cords affecting 2 joints or one palpable cord affecting 2 joints in the same finger may be injected in 2 locations at the same visit). Other cords could be treated at 30-day intervals.
- Collagenase Clostridium Histolyticum is only available through a managed distribution. Only enrolled, qualified healthcare providers may have access to CCH. Only enrolled healthcare sites may receive CCH orders.
- CORD I and CORD II are randomized, double-blind, placebo-controlled trials. Patients had to have a palpable cord and either a MP contracture between 20°-100° or PIP contracture between 20°-80° and were unable to simultaneously place the affected finger and palm flat on a table. If patients had several joints with contractures, one was selected as the primary joint for treatment. The primary endpoint was defined as reduction in contracture to 0-5 degrees 30 days after the last injection in all primary joints.
- JOINT I and JOINT II are open-label trials where all patients received CCH. The treatment protocol and entry criteria for these trials were similar to the CORD trials except that patients may receive up to 5 CCH injections (5 treatment cycles) with maximum of 3 per cord separated by at least 30 days.
- In the CORD trials, a significantly greater proportion joints treated with CCH achieved the primary endpoint than placebo (64% and 44.4% with CCH and 6.8% and 4.8% with placebo). In the JOINT trials, results were similar to those treated with CCH in the CORD trials (53% and 58% for JOINT I and JOINT II respectively). Across studies, MCP joints had a better response rate than PIP joints (65%-76.7% vs. 27%-41%). Less severe PIP joints had a higher response rate than those that were more severely affected.
- CORDLESS is a prospective 5-year follow-up study to determine long-term safety and recurrence, durability, and progression rates following CCH treatment from CORD I and II, JOINT I and II, and CORD I extension. Recurrence was defined as an increase in contracture $\geq 20^\circ$ with palpable cord after successful treatment with CCH. The 4-year cumulative recurrence rate was 42.1% of treated cords. Recurrence in the PIP joints was greater than the MCP joints (61.6% vs. 34.6%).

- MULTICORD is a 60 day, multicenter, open-label, phase 3b, unpublished trial which was conducted to evaluate the safety and efficacy of concurrent administration of 2 CCH injections into palpable cords of the same hand as well as to evaluate the effect of varying time to finger extension. A single injection in each of 2 affected joints, administered concurrently in the same hand, was associated with similar efficacy and frequency of adverse effects compared to single joint treatment, with the exception of a higher incidence of skin lacerations. Timing of the finger extension procedure did not affect clinical response or safety; however, there was a trend towards a lower rate of finger lacerations when finger extension were performed at 72 hours versus 24 or 48 hours.
- The most commonly reported adverse events in patients receiving CCH were swelling of the injected hand, contusion, injection site reaction, injection site hemorrhage, and pain in injected hand. Most events were mild to moderate in nature and resolved without intervention.
- In the CORD trials, there were 3 cases of flexor tendon rupture of the treated finger that occurred within 7 days of CCH injection. Two of the ruptures occurred in cords associated with the PIP joint of the little finger that led to a modified technique for injecting for cords affecting that area. Three-year post-marketing data report that of the 49, 078 injections given, there were 26 reports of tendon rupture, a rate of 0.05% (26/49078). Of 19 tendon ruptures with known finger/joint involved, 14 (75%) were in little finger; the joint and/or finger was unknown in remaining 7 reports.
- In the CORD trials, 15% of CCH-treated patients had pruritus compared to 1% receiving placebo. The incidence increased with administration of subsequent doses. One patient experienced an anaphylactic reaction in the MULTICORD trial. While no severe allergic reactions were observed in most clinical trials, patients developed IgE-anti-drug antibodies in greater proportions and higher titers with successive doses. It is recommended that healthcare providers be prepared to manage severe allergic reactions should they occur.
- In the 2 pivotal trials, ecchymosis/contusion or injection site hemorrhage occurred in 70% and 38% of patients treated with CCH respectively. The safety of using CCH in patients receiving anticoagulant/antiplatelet drugs (other than low-dose aspirin \leq 150mg daily) is unknown; therefore, use with caution in these patients or in patients with coagulation disorders.
- There are currently no data on administration of more than 3 injections of CCH per cord.
- For CCH-treated joints that have had a recurrence, there are preliminary data on retreatment with CCH in 51 patients.
- There are limited data on patients receiving more than 3 injections (up to 3 for the primary cord and the rest for other cords). There were 209/1082 (19%) patients who received 4-5 injections and 41 (3.8%) who received 6-8 injections.

Introduction

Dupuytren's Disease is a progressive disorder of pathologic collagen production and deposition. It begins with palpable nodules in the palm that later form collagen cords that thicken and shorten leading to flexion contractures that typically affect the metacarpophalangeal (MP) joint, proximal interphalangeal (PIP) joint, or both. The ring and little fingers are the most commonly affected.

The incidence of Dupuytren's Disease is greatest in those of northern European descent. The estimated world-wide prevalence among whites is 3-6%. The disease is more common in males than in females, in older individuals, and in those with a family history. Dupuytren's has been associated with smoking, alcoholism, diabetes, epilepsy, and HIV.

Treatment for flexion contractures are surgical (i.e. open fasciectomy, percutaneous (needle) fasciotomy or open fasciotomy). Surgery is recommended for those with functional impairment and MP joint contractures $>$ 30 degrees

or PIP joint contractures > 20 degrees. Post-operatively, patients will require hand physiotherapy. Surgery is usually successful; however, over time, extension and recurrence is likely.

Non-surgical treatments including radiotherapy, steroids, splinting, and topical vitamin A have been tried with limited success. The newest treatment, CCH hydrolyzes collagen resulting in lysis of collagen deposits and may result in enzymatic disruption of the cord.

Pharmacology/Pharmacokinetics

Collagenase Clostridium Histolyticum contains 2 microbial collagenases (AUX-I and AUX-II) which are isolated and purified from the fermentation of *Clostridium histolyticum* bacteria.

No quantifiable plasma levels of AUX-I or AUX-II were detected up to 30 days following a single 0.58mg injection into a Dupuytren's cord (n=20).

FDA-Approved Indication

- For treatment of adult patients with Dupuytren's contracture with a palpable cord
- For treatment of adult men with Peyronie's disease with a palpable plaque and curvature deformity of at least 30 degrees at the start of therapy (see addendum monograph)

Potential Off-Label Use

This section is not intended to promote any off-label uses. Off-label use should be evidence-based. See VA PBM-MAP and Center for Medication Safety's [Guidance on "Off-label" Prescribing](#) (available on the VA PBM Intranet site only).

- Treatment of Frozen Shoulder syndrome (Adhesive Capsulitis).

Current VA Formulary Alternatives

Not applicable

Dosage and Administration

The information contained in this monograph regarding dosing and administration is a partial summary.

Refer to the product package insert for detailed information on preparation, injection procedure, finger extension procedure, and post-injection instructions to patients.

- Administer by a healthcare provider experienced in injection procedures of the hand and in the treatment of patients with Dupuytren's contracture.
- The provided Medication Guide should be given to and read by the patient each time an injection is given.
- Dose: 0.58 mg per injection into a palpable cord with a contracture of a MP joint or PIP joint.
- Prior to use, the lyophilized powder must be reconstituted with the provided diluent. The volume of diluent needed for reconstitution differs for cords affecting the MP joints (0.39ml) and PIP joints (0.31ml). The volume of reconstituted collagenase to be injected is 0.25ml for MP joints and 0.20ml for PIP joints which each contain 0.58mg of drug.
- Place needle into cord in an area where the cord is maximally separated from the underlying flexor tendons and where the skin is not adhered to the cord. Once the needle is properly inserted into the cord, inject approximately 1/3 of the dose. Withdraw the tip of the needle from the cord and reposition it in a slightly more distal location (approx. 2-3mm) to the initial injection in the cord and inject another 1/3 of the dose. Withdraw and needle again and reposition it a third time proximal to the initial injection (approx. 2-3mm) and inject the final 1/3 of the dose into the cord.
- Administration of a local anesthetic prior to injection is not recommended as it may interfere with proper placement of the CCH injection.

- Approximately 24 to 72 hours after the injection, perform a finger extension procedure if contracture persists in order to facilitate cord disruption. Local anesthesia may be used at this time. If the first finger extension does not result in cord disruption, a 2nd and 3rd attempt may be tried
- If a MP or PIP contracture remains 4 weeks after the injection and finger extension procedure, the cord may be re-injected with a single 0.58mg dose with repeat finger extension procedures. Injections and finger extension procedures may be administered up to 3 times per cord at approximately 4-week intervals.
- Up to 2 cords may be treated in the same hand at a treatment visit (2 palpable cords affecting 2 joints OR one palpable cord affecting 2 joints in the same finger may be injected in 2 locations at the same visit). Other cords could be treated at 30-day intervals.
- Discard unused portion of reconstituted solution and diluent after injection. Do not store, pool, or use any vials containing unused reconstituted solution or diluent.
- Following finger extension procedure, the patient should be fitted with a splint to be worn at bedtime for up to 4 months. Patients should also be instructed to perform finger extension and flexion exercises several times a day for several months.

Dosage Form/Strength

Single-use glass vials containing 0.9mg of collagenase clostridium histolyticum as a sterile, lyophilized powder for reconstitution. The provided diluent for reconstitution comes as a single-use glass vial containing 3ml of 0.3mg/ml calcium chloride dehydrates in 0.9% sodium chloride.

Availability

Xiaflex is available for treatment of Dupuytren's contracture only through the XIAFLEX REMS Program.

- For detailed information go to www.xiaflexrems.com
- Xiaflex should be administered by a healthcare provider experienced in injection procedures of the hand and in the treatment of Dupuytren's contracture.
- Restricted distribution through specialty certified healthcare settings (e.g., pharmacies, practitioners, hospitals, outpatient settings)

Efficacy

There are 13 clinical trials; 2 pivotal trials (CORD I and CORD II) and 2 open-label trials (JOINT I and JOINT II) have been published. The published trials will be the focus of discussion. The remaining trials are briefly shown in **Table 1**.

In some of the supportive and open-label studies a patient could receive up to a total of 5 doses (up to 3 for the primary cord and the rest for other cords). Among the 1082 patients treated in the 12 trials, 116 (11%) received 5 doses and 41 (3.8%) received 6-8 injections.²

Table 1: Trials Evaluating CCH for Dupuytren's Contracture

Study	Injections or other procedure	Duration of study	Number of patients	% patients with clinical success of primary joint
Pivotal Trials (R, DB, PC)				
CORD I ¹	Up to 3 injections into 1 cord	90-days	0.58mg (n=204) PBO (n=104)	64 7
CORD II ²	Up to 3 injections into 1 cord	90-days	0.58mg (n=45) PBO (n=21)	44 5
Supportive Trials (R, DB, PC)				
Study 03 ⁴	Up to 3 injections into 1 cord	90-days	0.58mg (n=23) PBO (n=12)	91 0

Study 53	Up to 3 injections into 1 cord; if patients had untreated cords, may receive OL Xiaflex (up to 5 additional injections)	90-days	0.58mg (n=17) PBO (n=6)	77 0
Study 51	Up to 3 injections into 1 cord	90-days	0.58mg (n=5) PBO (n=2)	20 0
Study 02 ⁵	Dose ranging; 1 injection into 1 cord; may receive up to 4 additional OL injections q 4-6 weeks		0.58mg (n=23) 0.29mg (n=22) 0.145mg (n=18) PBO (n=17)	78 46 50 0
Open-label, uncontrolled safety studies				
JOINT I ³	Up to 5 injections (maximum 3 injections into 1 cord)	9-months	386	53
JOINT II ³	Up to 5 injections (maximum 3 injections into 1 cord)	9-months	201	58
Study 58	Up to 5 injections (maximum 3 injections into 1 cord)	9-month extension of CORD I (total 12 months)	286	
Study 04 ⁴	Up to 5 injections (maximum 3 injections into 1 joint); injections given q 4-6 weeks	14-months extension of study 03 (total 17 months)	19	
Study 55	1 injection into 1 cord	Single-dose PK study	16	
Study 52	May receive up to 5 injections	9-month extension of study 51 (total 12 months)	N/A	
Study 687 MULTICORD	2 injections in one hand at one visit (2 cords affecting 2 joints each injected or 1 cord affecting 2 joints in the same finger injected in 2 locations) Time of finger extension procedure was varied (24, 48, or 72 hours)	60-days	715	65% (MP joint) 29% (PIP joint)

Data for unpublished trials obtained from FDA docket or meeting abstracts.

CORD I and CORD II

CORD I and II were 90-day randomized, double-blind, placebo-controlled trials.^{1,2} Patients had to have a palpable cord and either a MCP contracture between 20°-100° or PIP contracture between 20°-80° and were unable to simultaneously place the affected finger and palm flat on a table. If patients had several joints with contractures, one was selected as the primary joint for treatment.

Patients were randomized 2:1 collagenase or placebo. Primary joints were stratified according to type 2:1 MP:PIP and according to the severity of joint contracture (for MP ≤ 50° and > 50°; for PIP ≤ 40° and > 40°).

Collagenase 0.58mg or placebo was injected into the affected cord. Patients were to return to clinic within 24 hours of the injection to determine if joint manipulation was needed to rupture the cord. If needed, the joint could be manipulated up to 3 times. Patients were asked to wear a splint nightly for up to 4 months.

Patients could undergo a maximum of 3 treatments (3 injections) administered at 30-day intervals. If the primary joint met the primary endpoint with 1-2 injections, a secondary joint could be treated. If the primary joint and a secondary joint met the primary endpoint with 1 injection each, a tertiary joint could be treated.

The primary endpoint (clinical success) was defined as reduction in contracture to 0-5 degrees of full extension 30 days after the last injection in all primary joints.

The mean age of enrolled patients was 63 years, 81% were males, 62.6% and 37.4% of treated joints were MCP and PIP respectively, baseline contracture was approximately 50°, and range of motion (full flexion minus full extension) approximately 44°. Normal range of motion is about 90° for MP joints and 100° for PIP joints.

The mean number of injections administered to the cord was 1.7±0.8. A significantly greater proportion of joints treated with CCH achieved the primary endpoint than joints treated with placebo. Metacarpophalangeal joints had a better response rate than PIP joints. Less severe joints had a higher response rate than those that were more severely affected. The percentage of patients achieving the primary endpoint after 1, 2, or 3 injections of CCH was fairly

evenly distributed. There was significantly greater improvement in range of motion with CCH versus placebo (**Table 2**). Refer to **Appendix 1** for study details and results of other endpoints.

In CORD I and CORD II, approximately 9.8% of patients had prior surgery for Dupuytren's contracture on the same finger as the primary joint treated with CCH. There was no difference in primary outcome between these patients and those that did not undergo prior surgery for the joint being treated with CCH.

Approximately half the patients who did not achieve the primary endpoint after the first injection did not receive a second injection either because the investigator could not find a palpable cord or the patient was satisfied with the result.

JOINT I and JOINT II

JOINT I and JOINT II were 9-month open-label trials where all patients received CCH.³ The treatment protocol and entry criteria for these trials were similar to the CORD trials except that patients may receive up to 5 CCH injections (5 treatment cycles) with maximum of 3 per cord separated by at least 30 days.

The mean age of enrolled patients was 63.7 years, 85% were males, total contracture index was 135 ± 105 , 38% had prior surgery for Dupuytren's, and 60.4% and 39.6% of treated joints were MCP and PIP respectively.

There were 879 joints treated with 1238 CCH injections. The mean number of injections per joint was 1.4 ± 0.7 (range 1-4). Results were similar to those treated with CCH in the CORD trials **Table 2**. Refer to **Appendix 2** for study details and results of other endpoints.

Table 2: Results of CORD and JOINT Trials

	CORD I		CORD 2		JOINT I	JOINT II
	CCH	PBO	CCH	PBO	CCH	CCH
Achieved 1° endpoint (%)						
• All joints	64	6.8	44.4	4.8	53	58
• MP joints	76.7	7.2	65	9.1	67	71
• PIP joints	40	5.9	28	0	27	41
Achieved 1° endpoint baseline low severity † (%)						
• MP joints	88.9	Not shown	70	14.3	Combined JOINT I AND II	
• PIP joints	80.9		40	0	81	
Achieved 1° endpoint baseline high severity§ (%)						
• MP joints	57.7	Not shown	65	0	Combined JOINT I AND II	
• PIP joints	22.4		25	0	39	
Patients achieving 1° endpoint [n/N (%)]						
• After first injection	79/203 (39)	1/103 (1)	12/45 (27)	1/21 (5)	Combined JOINT I AND II	
• After second injection	35/99 (35)	1/100 (1)	6/22 (27)	0/19 (0)	46	
• After third injection	16/45(36)	5/91(6)	2/8 (25)	0/18 (0)	25	
Increase in range of motion (degrees)						
• All joints	36±21	4±15	35±18	8±15	28.2±20	30.6±17
• MP joints	41±20	4±13	40±13	9±15	33.3±17	32.9±16
• PIP joints	28±22	5±19	32±20	7±16	18.9±22	27.5±19

†Low severity defined as $<50^\circ$ and $<40^\circ$ for MCP and PIP joints respectively

§High severity defined as $\geq 50^\circ$ and $\geq 40^\circ$ for MCP and PIP joints respectively

Recurrence

CORDLESS (Collagenase Option for Reduction of Dupuytren's Long-Term Evaluation of Safety Study) is a prospective 5-year follow-up study to determine long-term safety and recurrence, durability, and progression rates in adult patients with Dupuytren's following CCH treatment. Patients were included if they had received ≥ 1 CCH

injection and had ≥ 1 post-treatment assessments in any of the 5 previous studies (CORD I and II, JOINT I and II, and CORD I extension).^{8,9}

Recurrence was defined as an increase in contracture $\geq 20^\circ$ with palpable cord OR the need for further surgical or medical intervention after successful treatment (contracture $0-5^\circ$ of normal) with CCH.

There were 644 patients (1081 treated joints) enrolled in CORDLESS. Among the treated joints, 623/1081 (57.6%) were treated successfully (451 MCP/172 PIP), 302 had measurable improvement (152 MCP/150 PIP) and 156 were not effectively treated (45 MCP/111 PIP).

Table 3 shows the cumulative rate of recurrence from years 2- 4 after successful treatment. The PIP joints had a higher rate of recurrence than the MCP joints. Breakdown of cumulative recurrence rates according to baseline severity are shown in **Table 4**. MCP joints with less severe contraction at baseline had a slightly higher rate of recurrence than MCP joints with higher baseline severity. In contrast, PIP joints with less severe contraction at baseline had a lower recurrence rate.

Table 3: Cumulative Recurrence Rate (CORDLESS Trial)

	2-year	3-year	4 -year
Overall (%)	19.3	35	42.1
MCP joint (%)	13.6	27	34.6
PIP joint (%)	34.1	56	61.6

Table 4: Cumulative Recurrence by Baseline Severity

	Year 3		Year 4	
	MCP joint	PIP joint	MCP joint	PIP joint
Low Severity † n/N (%)	105/374 (28)	60/121 (50)	134/374 (36)	71/121 (58)
High Severity § n/N (%)	14/77 (18)	36/51 (71)	22/77 (29)	36/51 (71)

†Low severity defined as $<50^\circ$ and $<40^\circ$ for MCP and PIP joints respectively

§High severity defined as $\geq 50^\circ$ and $\geq 40^\circ$ for MCP and PIP joints respectively

Nondurability was defined as an increase in contracture $\geq 20^\circ$ with palpable cord OR the need for further surgical or medical intervention after measurable improvement ($\geq 20^\circ$ improvement in contracture, but not to $<5^\circ$) with CCH. Fifty percent (150/301) met the definition of nondurable by year 3.

Of the 156 joints that were considered as not effectively treated after CCH, 59 joints (15 MCP; 44 PIP) progressed (using the same definitions as for recurrence and nondurability) by year 3. Nondurability and progression data were not shown for year 4.

Based on historical surgery literature, the incidence of recurrence with CCH was not greater than that following fasciectomy or fasciotomy. There is a wide range of recurrence rates following surgery as it is dependent on the type of surgery, affected finger, and affected joint, follow-up period, and definitions used for recurrence.

Recurrence rates for surgical procedures after 3-4 years of follow-up are: limited fasciectomy 33-54%; dermofasciectomy 8.9-33%; total fasciectomy 10%; needle aponeurotomy 58-65%; fasciotomy 48-58%.¹⁰⁻¹²

Retreatment in those with prior clinical success

Among those who were originally successfully treated, 80/623 (13%) joints were subsequently treated between years 2-4 for “patient-reported” worsening of contracture. The most common interventions were retreatment with CCH or fasciectomy (**Table 5**).⁹

Table 5: Interventions for Worsening Contracture in Those with Prior Successful Treatment⁹

Total interventions	CCH	Fasciectomy	Needle aponeurotomy	Fasiotomy	Dermofasciectomy	Other
Year 2 (n)	15	0	9	3	0	3
Year 3 (n)	32	6	20	4	1	0
Year 4 (n)	38	18	12	5	1	2

More recently, 30-day interim data on retreatment with CCH for joints previously successfully treated are available for 51 patients (31 MCP and 20 PIP joints). Mean baseline contracture was 39.7° and 46.3° for MCP and PIP joints respectively.¹³

Of the 51 joints, 35 (69%), 12 (24%), and 4 (8%) received 1, 2, and 3 injections respectively. Clinical success, defined as contracture ≤5°, was achieved in 20 (65%) of MCP joints and 9 (45%) of PIP joints. Mean contracture was reduced by 83% and 69% for MCP and PIP joints respectively. For the remaining joints, either no palpable cord was felt to continue treatment or the patient was satisfied with the improvement and chose not to have further injections. The full study will follow patients for 1-year after their last injection.

Adverse Events (Safety Data)

The entire safety database included 1082 patients with 1780 Dupuytren's cords (2630 injections). Mean duration of safety follow-up was 9.5±4.6 months. From this database 443(41%) patients received 1 injection, 219 (20%) received 2 injections, 170 (16%) received 3 injections, and 250 (23%) received 4-8 injections. Cords injected may also include those that were not designated as primary cords.²

In the clinical trials, CCH was administered primarily by carefully selected hand surgeons (there were a limited number of orthopedic surgeons and rheumatologists) who were trained in the CCH administration technique and finger extension procedures. The manufacturer plans on marketing CCH to other surgical specialists (i.e., orthopedic, plastic, and general surgeons) and non-surgeons such as rheumatologists; therefore, the risks of adverse events could differ from that seen in the clinical trials.

Adverse Events

Patients receiving collagenase had more injection- and manipulation-related adverse events than those receiving placebo. Most adverse events were mild to moderate in nature and resolved without intervention within a median of 10 days. The most commonly reported AEs were peripheral edema (mostly swelling of the injected hand), contusion, injection site hemorrhage and reactions, and pain in the extremity (**Table 6**). There were no nerve injuries, or clinically meaningful adverse changes in grip strength or systemic allergic reactions reported in the CORD trials through day 90.

In the CORD trials, 3 patients discontinued the trial because of a drug-related AE (1 severe injection site pain, 1 dizziness, 1 complex regional pain syndrome).²

Table 6: Adverse Reactions Occurring in ≥ 5% of CCH Patients (CORD and JOINT Trials)

	CORD I and II		JOINT I and II	
	CCH (%) N=249	Placebo (%) N=125	CCH (%) N=587	Placebo (%) N=587
All adverse events	98	51	97	97
Edema peripheral	73	5	75	75
Contusion	70	3	60	60
Injection site hemorrhage	38	3	37	37
Injection site pain	-	-	42	42
Injection site reaction	35	6	-	-
Pain in extremity	35	4	38	38
Tenderness	24	0	25	25
Injection site swelling	24	6	27	27
Pruritus	15	1	10	10
Lymphadenopathy	13	0	7	7
Skin laceration	9	0	9	9
Lymph node pain	8	0	-	-
Erythema	6	0	-	-
Axillary pain	6	0	8	8
Blood blister	-	-	8	8
Ecchymosis	-	-	7	7
Injection-site vesicles	-	-	6	6

Serious Adverse Events (SAE)

In the CORD trials, there were 7 SAEs in the CCH group with 5 occurring in the injected extremity and 2 that did not involve the injected extremity. Among the 5 SAEs involving the injected extremity, there were 2 cases of tendon rupture, 1 case of complex regional pain syndrome, 1 flexor pulley rupture, and 1 ligament disorder. The first 4 events are thought to be related to CCH administration. No tendon ruptures were reported in the JOINT trials. See section on post-marketing safety for additional information on tendon ruptures.

In the open-label, uncontrolled studies, there were 6 SAEs reported involving the treated extremity. There was 1 additional case of tendon rupture, 1 sensory abnormality of the hand, 1 fracture of the tip of the finger with ligament tear (due to a farming accident), 1 tendonitis, 1 Boutonniere deformity, and 1 elective amputation of the little finger due to an unrelated traumatic event.

Because 2/3 tendon ruptures occurred in cords associated with the PIP joint of the little finger, a modified injection technique was introduced. This included instructions to avoid injecting more than 4mm distal to the palmar digital crease and NOT to insert the needle more than 2-3mm in depth when injecting cords associated with contractures of the PIP joint of the little finger.

Two SAEs classified as possibly or probably drug related were reported in the JOINT trials; deep vein thrombosis in the leg (n=1) and tendonitis near the injection site (n=1).

Deaths

There were no deaths, in the CORD trials through day 90. In the complete clinical development program, there were 7 deaths in patients receiving CCH. These deaths were believed to be due to the patient's underlying co-morbidities. The deaths occurred several months after the last CCH injection.

Immunogenicity

The majority of patients treated with CCH test positive for antibodies against AUX-I, AUX-II, or both after 30 days of the first injection (**Table 7**). In the CORD I trial, clinical efficacy was compared between patients positive for neutralizing antibodies (NAb) to AUX-I and AUX-II to those who were negative. In this trial, 6% and 10% of patients had a positive NAb to AUX-I and AUX-II respectively. There was no difference in the percentage of patients achieving the primary endpoint between those who were positive versus negative for NAb to AUX-I. The percentage of those achieving the primary endpoint was slightly lower for those positive for NAb to AUX-II compared to those who were negative (50% vs. 66%).² When looking at the larger clinical database, 10% and 21% of CCH-treated patients developed NAb to AUX-I and AUX-II respectively. There was no correlation between antibody frequency, antibody titers, or neutralizing status to efficacy or adverse reactions.

Table 7: Proportion of Patients Testing Positive for AUX-I and AUX-II Antibodies (CORD and JOINT)

	CORD I	CORD II	JOINT I	JOINT II
AUX-I (%)	85.8	95.2	93	92
AUX-II (%)		88.2	85	89

Because CCH is immunogenic, allergic reactions are expected. Of interest is the effect repeated exposure has on the risk of allergic reactions. In the CORD trials, the proportion of patients who experienced mild allergic reactions with CCH increased with repeated treatments compared to placebo. When evaluating pruritus in the CORD I study, the percentage of patients experiencing pruritus was 5% after 1 injection, 15% after 2 injections, and 44% after 3 injections. A similar trend was seen in study 59. In the 13 submitted studies, there was only one case of severe allergic reaction reported (anaphylactic reaction in MULTICORD).

There is a theoretical concern that protein components AUX-I and AUX-II may have the potential to cross-react with human matrix metalloproteinases (MMPs). Homology of AUX-I and AUX-II to human MMPs ranges from 24-53%. In vitro cross-reactivity was tested using the sera of 5 patients. One of the 5 patients had anti-AUX-II antibodies that cross-reacted with relevant human MMPs; there was no cross-reactivity with anti-AUX-I antibodies.

A post-marketing study is required using sera from patients who have received multiple CCH doses to evaluate the potential for cross-reactivity.

Post-marketing Safety Information

Three-year (2/2/10-2/2/13) US/EU post-marketing AE data are available. Approximately 49,078 CCH injections have been given; there were 1732 AEs reported in 846 patients. Most common AEs were localized and non-serious reactions.¹⁴

Palmar & digital skin tears was the most commonly reported AE 228/1732 (13.2%). Most were lacerations and skin lesions that healed without intervention. There were 19 skin grafts reported for the 228 with skin tears post-manipulation; 10/19 (53%) of skin grafts were for PIP contracture in the little finger.

Table 8: AEs Reported ≥3% (3-year Post-Marketing Surveillance)¹⁴

	Post-Market AE n (%)**	Report rate/ 1000 doses
Skin tear	228 (13.2)	4.6
Contusion	168 (9.7)	3.4
Peripheral edema	164 (9.5)	3.3
Drug ineffective	106 (6.1)	2.2
Pain in extremity	80 (4.6)	1.6
Swelling, unspecified	67 (3.9)	1.4
Lymphadenopathy	53 (3.1)	1.1
Hematoma	49 (2.8)	1.0
Injection site pain	47 (2.7)	1.0
Injection site hematoma	45 (2.6)	0.9

** Percent based on total number (n=1732) of AEs reported

Of the 49,078 injections given, there were 26 reports of tendon rupture, a rate of 0.05% (26/49078). Of 19 tendon ruptures with known finger/joint involved, 14 (75%) were in little finger; the joint and/or finger was unknown in remaining 7 reports. In the clinical trials, there were 3 tendon ruptures and pulley injury.

Skin lacerations occurred in 160/715 (22.4%) of patients treated in MULTICORD in addition to the aforementioned episode of anaphylaxis following CCH administration.

Contraindications

Patients with a history of severe allergic reaction to Xiaflex or to collagenase used in any other therapeutic application or application method

Warnings and Precautions

There have been 3 cases of flexor tendon rupture of the treated finger that occurred within 7 days of CCH injection. Care must be taken to avoid injection of CCH into tendons, nerves, blood vessels, ligaments or other collagen-containing structures of the hand; inject only into the collagen cord with the MP or PIP joint contracture. If injecting a cord affecting the PIP joint of the little finger, needle insertion should not be more than 2-3mm in depth and avoid injecting more than 4mm distal to the palmar digital crease.

Other serious drug-related local AEs include pulley rupture, ligament injury, complex regional pain syndrome, and sensory abnormality of the hand.

In the CORD trials, 15% of CCH-treated patients had pruritus compared to 1% receiving placebo. The incidence increased with administration of subsequent doses. Although no severe allergic reactions were observed in the clinical trials, patients developed IgE-anti-drug antibodies in greater proportions and higher titers with successive doses. It is recommended that healthcare providers be prepared to manage severe allergic reactions should they occur.

In the CORD trials, ecchymosis/contusion or injection site hemorrhage occurred in 70% and 38% of patients treated with CCH respectively. The safety of using CCH in patients receiving anticoagulant/antiplatelet drugs (other than

low-dose aspirin \leq 150mg daily) is unknown as these patients were excluded from the trials; therefore, use with caution in these patients or in patients with coagulation disorders.

Look-alike/Sound-alike (LASA) Error Risk Potential

As part of a JCAHO standard, LASA names are assessed during the formulary selection of drugs. Based on clinical judgment and an evaluation of LASA information from four data sources (Lexi-Comp, USP Online LASA Finder, First Databank, and ISMP Confused Drug Name List), the following drug names may cause LASA confusion.

Table 9: LASA Error Risk Potential

NME Drug Name	Lexi-Comp	First DataBank	USP	ISMP	Clinical Judgment
Collagenase Clostridium Histolyticum	Topical collagenase	None	None	None	None
Xiaflex™	Zanaflex	None	None	Zanaflex	Xopenex Zoladex Xifaxan Xanax

Drug Interactions

Use with caution in patients receiving concomitant anticoagulants (excluding low-dose aspirin) as described under Warnings and Precautions.

Cost

Please refer to VA pricing sources for updated information.

Summary

Collagenase Clostridium Histolyticum is the first approved non-surgical treatment for Dupuytren's contracture.

- Collagenase Clostridium Histolyticum should be reserved for patients with joint contractures with a palpable cord that result in impaired hand function.
- It should not be used for those with mild or early disease. In the pivotal trials, entry criteria included fixed flexion contraction of the MP joint between 20-100 degrees or fixed flexion contraction of PIP joint between 20-80 degrees.
- Up to 2 cords may be treated in the same hand at a treatment visit (2 palpable cords affecting 2 joints or one palpable cord affecting 2 joints in the same finger may be injected in 2 locations at the same visit); other cords could be treated in 30-day intervals. A single cord may receive up to 3 injections at 30-day intervals.;
- Collagenase Clostridium Histolyticum is only available through the XIAFLEX REMS Program and is restricted to providers experienced in injection procedures of the hand AND treatment of Dupuytren's contractures (i.e., hand surgeons, orthopedic surgeons).
- There are currently no data on more than 3 injections per cord. Preliminary data are available for retreatment with CCH for previously CCH-treated joints that have had a recurrence.

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Collagenase Clostridium Histolyticum Monograph

Appendix 1: Pivotal Clinical Trials (CORD I and II)

	Entry Criteria	Treatment	Demographics/Baseline Characteristics	Results	
				CCH	Placebo
Hurst 2009 CORD I R, DB, PC 16 U.S. centers 90 days N=308	<p>Inclusions:</p> <ul style="list-style-type: none"> Dupuytren's disease ≥ 18 years old MP contractures between 20°-100° or PIP contractures between 20°-80° Unable to simultaneously place the affected finger and palm flat on a table Women had to be post-menopausal or using contraception <p>Exclusions:</p> <ul style="list-style-type: none"> Thumb involvement Breast-feeding or pregnancy Bleeding disorder Recent stroke Previous treatment of primary joint within 90days before beginning of study Collagenase treatment or treatment with any investigational drug within 30 days before beginning of study Use of tetracycline derivative within 14 days before beginning of the study Use of anticoagulant within 7 days before beginning of study Allergy to collagenase Chronic muscular, neurologic, or neuromuscular disorder affecting the hands 	<p>2:1 randomization collagenase or placebo</p> <p>Primary joints were stratified according to type</p> <p>2:1 MP:PIP and according to the severity of joint contracture (for MP ≤ 50° and > 50°; for PIP ≤ 40° and > 40°)</p> <p>Treatment arms</p> <p>CCH 0.58mg into affected cords (n=204)</p> <p>Placebo containing TRIS and sucrose in diluent (n=104)</p> <p>If needed, joints were manipulated up to 3 times the day after the injection in an effort to rupture cord</p> <p>Patients wore a splint to wear nightly for up to 4 months</p> <p>Patient could undergo a maximum of 3 treatments (3 injections) given at 30-day intervals</p> <p>If the primary joint met the primary endpoint with 1-2 injections, a second joint could be treated</p> <p>If the primary joint and a secondary joint met the primary endpoint with 1 injection each, a tertiary joint could be treated</p>	<p>Values shown for CCH; placebo respectively</p> <p>Age (yrs): 62.3 ± 9.7; 63.3±9.1</p> <p>Males (%): 83.8; 71.2</p> <p>White (%): 99.5; 100</p> <p>Family history of Dupuytren's (%): 41.7; 51</p> <p>Age at diagnosis (yrs): 53±12.6; 52.6±12.2</p> <p>Total contracture index (degrees): 149.1 ± 127.6; 149.3±111.4</p> <p>Hand with ≥ 1 contracture (% pts.):</p> <ul style="list-style-type: none"> Left hand: 26.5; 26.9 Right hand: 33.8; 38.5 Both hands : 39.7; 34.6 <p>Affected joints per patient (no)</p> <ul style="list-style-type: none"> Total: 3 ± 2.2; 3 ± 2.1 MP joints: 1.6 ± 1.5; 1.7±1.4 PIP joints: 1.4 ± 1.3; 1.3±1.3 <p>Prior fasciotomy or fasciectomy (%): 35.8; 42.3</p> <p>Prior fasciotomy or fasciectomy on same finger as primary joint (%): 8</p> <p>ROM –degrees</p> <ul style="list-style-type: none"> All primary joints: 43.9; 45.3 Primary MP joints: 42.6; 45.7 Primary PIP joints: 46.4; 44.4 <p>Primary MP joints > 50° of full extension (%): 39; 39</p> <p>Primary PIP joints > 40° of full extension (%): 70; 74</p> <p>Contracture degree</p> <ul style="list-style-type: none"> All primary joints: 50±20; 49±20 Primary MP joints: 48±20; 45±21 Primary PIP joints: 54±19; 57±17 <p>Mean ± SD</p> <p>Total contracture index= sum of the fixed-flexion contractures (≥ 20degrees caused by a cord) in all 16 joints measured at screening</p>	<p>Completed study (%)</p> <p>d/c due to AE (n)</p> <p>Achieved 1° endpoint (%)</p> <ul style="list-style-type: none"> All primary joints MP joints PIP joints <p>Median time to reach 1° endpoint (days)</p> <ul style="list-style-type: none"> All primary joints MP joints PIP joints <p>Patients achieving 1° endpoint [n/N (%)]</p> <ul style="list-style-type: none"> After first injection After second injection After third injection <p>Mean change in ROM (degrees)</p> <ul style="list-style-type: none"> All primary joints MP joints PIP joints <p>MP joints meeting 1° endpoint according to baseline severity (%)</p> <ul style="list-style-type: none"> ≤ 50 degrees > 50 degrees <p>PIP joints meeting 1° endpoint according to baseline severity (%)</p> <ul style="list-style-type: none"> ≤ 40 degrees > 40 degrees <p>≥50% reduction in contracture (%)</p> <ul style="list-style-type: none"> All primary joints MP joints PIP joints <p>Contracture degree 30 days after injection (up to 3 injections)</p> <ul style="list-style-type: none"> All primary joints Primary MP joints Primary PIP joints <p>Number of injections</p> <p>Recurrence at 90 days</p>	<p>94</p> <p>2</p> <p>64</p> <p>76.7</p> <p>40</p> <p>NC</p> <p>36</p> <p>NC</p> <p>79/203 (39)</p> <p>35/99 (35)</p> <p>16/45(36)</p> <p>36.7</p> <p>40.6</p> <p>29</p> <p>88.9</p> <p>57.7</p> <p>80.9</p> <p>22.4</p> <p>84.7</p> <p>94</p> <p>67.1</p> <p>12±19</p> <p>8±8</p> <p>22±22</p> <p>444 injections in 204 patients</p> <p>297 injections in 104 patients</p> <p>None</p> <p>N/A</p>

Collagenase Clostridium Histolyticum Monograph

Appendix 1 continued

	Entry Criteria	Treatment	Demographics/Baseline Characteristics	Results	
				CCH	Placebo
Gilpin 2010 CORD II R, DB, PC Australian centers 90 days + 9 months N=66	Same as CORD I	Double-blind phase same as CORD I CCH (n=45) PBO (n=21) During the 9-month open-label phase treatment was at the discretion of the investigator. Patients from the double-blind phase who still needed CCH could receive up to 5 additional CCH injections (including those who received PBO, did not achieve clinical success with <3 CCH injections, had other Duputren's cords that were not injected with CCH)	Values shown for CCH; placebo respectively Age (yrs): 63; 65.5 Age ≥ 65 years (%): 44; 57 Males (%): 87; 81 White race (%): 100/100 Duration of symptoms (yrs): 5.7; 5.7 Family history of Dupuytrens (%): 49; 43 Total contracture index (degrees): 175±107; 150± 84 Hand with ≥ 1 contracture (% pts.): <ul style="list-style-type: none">• One hand: 51; 43• Both hands: 49; 57 Affected joints per patient (no) <ul style="list-style-type: none">• Total: 3.4±2.3; 3.0±1.5• MP joints: 1.5 ± 1.6 ; 1.5 ± 1.5• PIP joints: 2.0 ± 1.6; 1.4±1.2 Patients with prior surgery for Dupuytren's contracture (%): 53; 52 Prior surgery on same finger as primary joint (%): 18 ROM –degrees (CCH; PBO): <ul style="list-style-type: none">• All primary joints: 40±15; 44±16• Primary MP joints: 40±12; 41±21• Primary PIP joints: 41±18; 47±10 Primary MP joints > 50° of full extension (%): 50; 36 Primary PIP joints > 40° of full extension (%): 80; 80 Contracture degree <ul style="list-style-type: none">• All primary joints: 53±15; 50±16• Primary MP joints: 50±14; 47±18• Primary PIP joints: 56±15; 54±13 Normal range of motion is about 90° for MP joints and 100° for PIP joints	Completed study (%) d/c due to AE (n) Achieved 1° endpoint (%) <ul style="list-style-type: none">• All primary joints• Primary MP joints• Primary PIP joints Patients achieving 1° endpoint [n/N (%)] <ul style="list-style-type: none">• After first injection• After second injection• After third injection Change from baseline in ROM 30 days after injection (degrees) <ul style="list-style-type: none">• All primary joints• Primary MP joints• Primary PIP joints MP joints meeting 1° endpoint according to baseline severity (%) <ul style="list-style-type: none">• ≤ 50 degrees• > 50 degrees PIP joints meeting 1° endpoint according to baseline severity (%) <ul style="list-style-type: none">• ≤ 40 degrees• > 40 degrees Contracture degree 30 days after injection (up to 3 injections) <ul style="list-style-type: none">• All primary joints• Primary MP joints• Primary PIP joints ≥50% reduction in contracture (% joints) <ul style="list-style-type: none">• All primary joints	100 0 44.4 65 28 12/45 (27) 6/22 (27) 2/8 (25) 35±18 40±13 32±20 70 65 40 25 17±19 7±15 24±22 77.8 44±20 43±23 48±18 14.3 0 0 14.3 0 0 0 14.3

Primary endpoint = reduction in contracture to 0-5 degrees 30 days after the last injection in all primary joints.

Efficacy results are based on primary joints

Recurrence = increase in joint contracture to 20 degrees or more in the presence of a palpable cord any time during the study

Appendix 2: JOINT I and II Trials

	Entry Criteria	Treatment	Demographics/Baseline Characteristics	Results		
				JOINT 1 (292 joints)	JOINT II (587 joints)	
Without 2013 JOINT I and JOINT II Open-label US, Europe, Australian centers 9 months N=587 (JOINT I n=201; JOINT II n=386)	<p>Inclusions: Dupuytren's disease ≥ 18 years old MP contractures between 20°-100° or PIP contractures between 20°-80°</p> <p>Exclusions similar to CORD trials</p>	<p>May receive up to 5 CCH 0.58mg injections (5 treatment cycles) with maximum of 3 per cord separated by at least 30 days</p> <p>Only 1 cord injected within given treatment cycle</p> <p>If needed, joints were manipulated up to 3 times the day after the injection in an effort to rupture cord</p> <p>Patients wore a splint to wear nightly for up to 4 months</p>	<p>Combined values for both studies</p> <p>Age (yrs): 63.7±9.7 Males (%): 85 White race (%): 100 Duration of symptoms (months): 62.6±69.3 Family history of Dupuytrens (%): 42 Total contracture index (degrees): 135.1±106</p> <p>Hand with ≥ 1 contracture (% pts.):</p> <ul style="list-style-type: none"> Left hand: 29 Right hand: 36 Both hands: 35 <p>Affected joints per patient (no)</p> <ul style="list-style-type: none"> Total: 2.8±2.0 (range 0-13) MP joints: 1.5 ± 1.3 (range 0-8) PIP joints: 1.2 ± 1.3 (range 0-7) <p>No prior tx for Dupuytren's (%): 58 Prior surgery for Dupuytren's (%): 38 Physician rating of severity as mild/moderate/severe (%): 25/51/24</p>	<p>Treatment disposition</p> <p>Joints treated (n) 879 joints (531 MCP; 348 PIP) No. of injections (n) 1238 injections Mean injections/cord (n) 1.4±0.7 (range 1-4) % pts with 1/2/3/4-5 joints treated 62/28/8/2</p> <p>Achieved 1° endpoint (%)</p> <ul style="list-style-type: none"> All joints 53 58 MP joints 67 71 PIP joints 27 41 <p>Patients achieving 1° endpoint (%) Combined JOINT I AND II</p> <ul style="list-style-type: none"> After first injection 46 After second injection 25 After third injection 26 <p>Change from baseline in ROM 30 days after injection (degrees)</p> <ul style="list-style-type: none"> All primary joints 28.2±20 30.6±17 Primary MP joints 33.3±17 32.9±16 Primary PIP joints 18.9±22 27.5±19 <p>MP joints meeting 1° endpoint according to baseline severity (%) Combined JOINT I AND II</p> <ul style="list-style-type: none"> ≤ 50 degrees 81 > 50 degrees 39 <p>PIP joints meeting 1° endpoint according to baseline severity (%) Combined JOINT I AND II</p> <ul style="list-style-type: none"> ≤ 40 degrees 51 > 40 degrees 25 <p>Change in contracture from baseline (%)</p> <ul style="list-style-type: none"> All primary joints 66.8±41 75.4±32 Primary MP joints 81.7±28 85.2±23 Primary PIP joints 40±47 61.6±37 <p>≥50% reduction in contracture (% joints)</p> <ul style="list-style-type: none"> All joints 72 79 MP joints 86 90 PIP joints 47 63 <p>Recurrence (≥20°contracture after successful treatment) n/N(%) 19/497 (4)</p>		