Collagenase Clostridium Histolyticum (Xiaflex™) for Peyronie’s Disease

National Drug Monograph Addendum

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  Documents will be placed in the Archive section when the information is deemed to be no longer current.*

**Introduction**

Collagenase Clostridium Histolyticum (CCH) has been approved for use in Peyronie’s Disease (PD). Peyronie’s disease is a localized connective tissue disorder of the tunica albuginea of the penis characterized by formation of a fibrotic lesion or plaque causing penile deformity such as penile curvature.

There are 2 phases of the disease: an acute inflammatory phase characterized by increased proliferation of fibroblasts in the tunica albuginea and a fibrotic/calcifying phase with excessive deposition of collagen and formation of a fibrotic lesion or plaque (disease stabilization).

Men with PD are at risk for depression, lowered self-esteem, issues with body-image, and relationship problems. Peyronie’s disease is managed medically or surgically. Medical treatments that have been used include pentoxifylline, potassium para-aminobenzoate, intralesional therapy using verapamil or interferon, and topical verapamil with clinical studies showing inconsistent results.

Collagenase Clostridium Histolyticum is FDA approved for treatment of adult men with PD with a palpable plaque and curvature deformity of at least 30 degrees at the start of therapy

Collagenase Clostridium Histolyticum is available through a managed distribution system. It is required that the pharmacy or healthcare system enroll in the program in order to receive shipments of CCH. Prescribers must be certified by enrolling and completing training in the administration of CCH treatment for Peyronie’s disease. For detailed information go to [www.xiaflexrems.com](http://www.xiaflexrems.com)

**Dosing**

CCH should be administered by healthcare providers experienced in the treatment of male urological diseases and who have completed the manufacturers required training for use in Peyronie’s disease.

The dose per injection is 0.58mg administered into a Peyronie’s plaque. If more than 1 plaque is present, inject into the plaque causing the curvature deformity.

A treatment course consists of a maximum of 4 treatment cycles. Each treatment cycle consist of 2 CCH injection procedures. The second injection procedure is performed 1-3 days after the first; 1-3 days after the second injection procedure, the penile modeling procedure is performed.

The interval between treatment cycles is approximately 6 weeks. The treatment course consists of a maximum of 8 injections and 4 penile modeling procedures. The safety of more than 1 treatment course is not known.

If the curvature deformity is <15 degrees after the first, second, or third treatment cycle, or if the healthcare provider determines that further treatment is not clinically indicated, then subsequent treatment cycles should not be given.

Please refer to the product package insert for detailed instructions on identification of the treatment area, injection procedure, dose preparation, and penile modeling procedure.

Safety of more than 1 treatment course is unknown.

**Efficacy**

There are 4 Phase 2 studies and 3 Phase 3 studies (**Table 1**). The phase 2 study 801 and the phase 3 studies 803 and 804 (IMPRESS I and IMPRESS II) are published. IMPRESS I and IMPRESS II are identically designed trials and will be the focus of this review.

**Table 1: Clinical Trials**

|  |  |  |
| --- | --- | --- |
|  | **Phase 2** | **Phase 3** |
| **1030-PEY** | **1035-PEY** | **Study 801** | **Study 805** | **Study 802** | **Study 803****IMPRESS I** | **Study 804****IMPRESS II** |
| Design | Open-label | Open-label | R, DB,PC | Open-label(p-kinetic) | Open label | R, DB, PC | R, DB, PC |
| n | 25 (CCH) | 10 (CCH) | 111 (CCH)36 (PBO) | 20 (CCH) | 237 (CCH) | 277 (CCH)140 (PBO) | 274 (CCH)141 (PBO) |

Abbreviations: DB=double-blind; CCH=collagenase clostridium histolyticum; PBO=placebo; PC=placebo-controlled; R=randomized

To be eligible for the study, the following inclusion criteria had to be met: healthy males ≥ 18 years old; diagnosis of PD for ≥ 12 months with evidence of stable disease; penile curvature of ≥30 degrees in dorsal, lateral, or dorsal/lateral plane; in stable relationship with female partner/spouse and willing to have vaginal intercourse with that partner/spouse. Patients were stratified according to degree of curvature (30-60 and 61-90) and were randomized 2:1 to CCH: placebo.

Key exclusion criteria include curvature <30 or >90 degrees, ventral curvature, calcified plaque that would prevent proper injection, received anticoagulant medication (excluding daily ASA ≤165mg or OTC NSAID ≤ 800mg) 7 days before each dose of study drug, surgery, oral/topical /intralesional agents within 3 months, extracorporeal shock wave therapy within 6 months, use of mechanical devices within 2 weeks (see **Appendix** for complete list of exclusion criteria).

Patients received CCH 0.58mg or an identical placebo for up to 4 treatment cycles. Each treatment cycle included 2 injections with an interval of 24-72 hours between injections.

Approximately 24-72 hours after the 2nd injection, patients underwent penile plaque modeling (using plaque as fulcrum point, investigator applied firm steady pressure to elongate and stretch the penis and held in this position for 30 seconds). This procedure was repeated 3 times. Patients were instructed to perform the modeling procedure at home 3 times daily using similar procedure during the 6-week period between each treatment cycle.

The treatment cycle was repeated after 6 weeks for up to 4 treatment cycles. After the 1st treatment cycle, subsequent cycles were not administered if curvature abnormality was reduced to <15 degrees or further treatment was not clinically indicated.

The mean age of patients was approximately 57 years, 96% Caucasian, mean PD history of 4.1 years, mean penile curvature of 50 degrees (77% with curvature deformity between 30-60 degrees), and approximately 50% had a history of PD.

The co-primary endpoints were percent change from baseline in penile curvature and change from baseline in the Bother domain score of the Peyronie’s Disease Questionnaire (PDQ). The PDQ is a questionnaire used to assess the psychosexual impact of PD and requires that the patient has had vaginal intercourse within the last 3 months. The questionnaire was developed by the manufacturer and is comprised of 15 questions divided into 3 subscale domains (psychological and physical symptoms, penile pain, and symptom bother). Each subscale domain is scored separately with higher scores representing greater negative impact. The PD symptom bother domain has 4 questions each graded on a 0-4 scale (4=very severe); the highest score for this domain is 16. The range of scores for the psychosocial and physical symptoms domain is 0-24 and 0-30 for the penile pain domain. Baseline PDQ bother domain score was 7.5 and 7.8 for the CCH and placebo groups respectively.

In the CCH and placebo groups, 78.8% and 87.9% of patients respectively received all 8 injections. Compared to placebo, significantly greater improvement was seen with CCH for both endpoints (**Table 2**). See **Appendix** for results of secondary endpoints.

**Table 2: Results of Primary Endpoints**

|  |  |  |
| --- | --- | --- |
|  | **CCH** | **PBO** |
| Penile curvature at 52 weeks (degrees) | 33.1±16.8\* | 40±16.2 |
| Change in curvature (%) | -34\* | -18.2 |
| Change in PDQ bother domain score | -2.8±3.8\* | -1.8±3.5 |

\*Significant vs. placebo

Subgroup analyses showed that similar improvements in penile curvature and PD symptom bother score occurred regardless of age, concomitant diabetes, history of penile trauma, severity of curvature (30-60 vs. 61-90 degrees), duration of disease or degree of plaque calcification (no calcification, non-contiguous stippling, contiguous stippling that did not interfere with injection).

**Safety**

In the 52-week trials, treatment-related adverse events (AEs) local to the penis and groin occurred in 84.2% and 36.3% of patients treated with CCH and placebo respectively. Adverse events were considered to be mild-moderate; 79% resolved without intervention within 14 days. Ten out 551 (1.8%) and 4/281 (1.4%) of patients receiving CCH and placebo respectively, discontinued treatment due to an AE. The most frequently reported AEs in CCH-treated patients were penile ecchymosis, penile swelling, and penile pain (**Table 3**).

The safety database for CCH in PD includes 6 completed and 1 interim study and includes those patients who received ≥ 1 injection (n=954) during phase 2 and 3 trials. There were 122/954 (12.8%) patients who discontinued the study; among these, 17 were due to an AE. The majority of patients (93.7%) reported at least 1 treatment-related nonserious AE (penile or injection site). There were 58 (6.1%) patients who experienced at least 1 nonfatal serious AE; 50 were considered not to be treatment related and 8 were considered treatment related (penile hematoma (n=4), corporal rupture (n=4). There were 3 deaths in the CCH groups and none in the placebo groups. The deaths were considered unrelated to treatment.

**Table 3: Adverse Events (%) Occurring in ≥1% of CCH-Treated**

**Patients in 52-week Trials**

|  |  |  |
| --- | --- | --- |
|  | **CCH (n=551)** | **Placebo (n=281)** |
| All tx-related AEs local to penis/groin | 84.2 | 36.3 |
| Penile hematoma | 65.5 | 19.2 |
| Penile swelling | 55 | 3.2 |
| Penile pain | 45.4 | 9.3 |
| Penile ecchymosis | 14.5 | 6.8 |
| Blood blister | 4.5 | 0 |
| Penile blister | 3.3 | 0 |
| Pruritus genital | 3.1 | 0 |
| Painful erection | 2.9 | 0 |
| Erectile dysfunction | 1.8 | 0.4 |
| Skin discoloration | 1.8 | 0 |
| Procedural pain | 1.6 | 0.7 |
| Injection site vesicles | 1.3 | 0 |
| Localized edema | 1.3 | 0 |
| Dyspareunia | 1.1 | 0 |
| Injection site pruritus | 1.1 | 0 |
| Nodule | 1.1 | 0 |
| Injection site pain | 1.1 | 0 |

Data obtained from product package insert

*Serious Adverse Events (SAEs)*

In the 52-week trials, there were 6 SAEs; corporeal rupture (n=3) and penile hematoma (n=3). One penile hematoma resolved without intervention, one resolved with aspiration, and one was successfully treated with surgery. The 3 corporeal ruptures were successfully treated with surgery.

In the larger database of controlled and uncontrolled clinical trials, corporeal rupture was reported in 5/1044 (0.5%) and severe penile hematoma in 39/1044 (3.7%) of patients.

*AUX-I and II antibodies*

After the first treatment cycle, 75% and 53.4% of CCH-treated patients had positive AUX-1 and AUX-II antibodies respectively. By week 52, approximately 99% of patients were positive for AUX-I and II antibodies respectively. There were no systemic immunologic events reported.

**Contraindications**

* Treatment of Peyronie’s plaques that involve the penile urethra due to potential risk to the urethra
* History of severe allergic reaction to CCH

**Warnings and Precautions**

* Corporal rupture (penile fracture) was reported in 5/1044 (0.5%) of patients in controlled and uncontrolled clinical trials.
* In 9/1044 (0.9%) of CCH-treated patients, a combination of penile ecchymosis or hematoma, sudden penile detumescence, and /or a penile popping sound or sensation was reported, and in these cases, a diagnosis of corporal rupture cannot be excluded. These patients were managed without surgical intervention; however, long-term consequences are unknown.
* Severe penile hematoma was reported in 39/1044 (3.7%) of patients.
* Prompt evaluation is necessary in patients who have signs or symptoms that may reflect serious injury to the penis in order to assess for corporal rupture or severe penile hematoma, which may require surgical intervention.
* Injection of CCH into collagen-containing structures such as the corpora cavernosa of the penis may result in damage and possible injury such as corporal rupture. Therefore inject CCH only into the Peyronie’s plaque; care should be taken to avoid injecting into the urethra, nerves, blood vessels, corpora cavernosa or other collagen-containing structures of the penis.
* Because of these risk, CCH is available only through the **XIAFLEX REMS Program**
	+ Prescribers must be certified by enrolling and completing training in the administration of CCH treatment for Peyronie’s disease
	+ Healthcare sites must be certified with the program to ensure CCH is only dispensed for use by certified prescribers
* In the 2 Phase 3 trials, 4% of CCH-treated versus 1% of placebo-treated patients had localized pruritus after up to 4 treatment cycles (involving up to 8 injection procedures). The incidence of pruritus was similar after each injection regardless of the number of injections administered. There is 1 report of an anaphylactic reaction in a post-marketing clinical study in a patient who had previous exposure to CCH for treatment of Dupuytren’s contracture. Healthcare provides should be prepared to address severe allergic reactions following CCH administration.
* In the 2 Phase 3 trials, 65.5% of CCH-treated patients developed penile hematoma and 14.5% developed penile ecchymosis. Patients with abnormal coagulation disorders or who were receiving anticoagulants (except for low-dose aspirin up to 150mg/day) were excluded from the clinical trials. The safety and efficacy of CCH in patients receiving anticoagulant medications (other than low-dose aspirin) within 7 days prior to CCH administration is not known. Therefore, it is recommended to avoid use of CCH in patients with coagulation disorders or receiving concomitant anticoagulants (except for low-dose aspirin)

**Cost**

Please refer to VA pricing sources for updated information.

**Conclusion**

Collagenase Clostridium Histolyticum is the first FDA approved drug for the treatment of PD. It is indicated for treatment of adult men with PD with a **palpable plaque** and **curvature deformity of at least 30 degrees** at the start of therapy. In the pivotal trials, study entry criteria also included that patient was in the stable phase of Peyronie’s disease. They were excluded if they had ventral curvature deformity, isolated hourglass deformity or a calcified plaque that could interfere with the injection technique.

In the pivotal trials, the mean decrease in curvature was 17 and 10 degrees for CCH and placebo respectively from a mean baseline of 50 degrees at 52 weeks. Because of safety concerns, CCH is only available through the XIAFLEX REMS Program and is restricted to providers specializing in the treatment of male urological diseases. Use of this agent should take into consideration the modest benefits, potential risks, intensive treatment regimen, and high cost.

**References**

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**Appendix: IMPRESS I and IMPRESS II**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Entry Criteria** | **Treatments** | **Demographic/ Baseline Information** | **Results** |
| Gelbard 2013Integrated results of 2 Phase 3 trialsR, DB, PC1-year | **Inclusions**Healthy males ≥ 18 years oldDiagnosis of PD for ≥ 12 months with evidence of stable diseasePenile curvature of ≥30° in dorsal, lateral, or dorsal/lateral planeIn stable relationship with female partner/spouse and willing to have vaginal intercourse with that partner/spouse**Exclusions**Penile curvature <30° or >90°; any conditions affecting the penis (e.g., chordee in the presence or absence of hypospadias, thrombosis of the dorsal penile artery, infiltration by benign or malignant mass or infection, ventral curvature, presence of sexually transmitted disease); known active Hep B or C; known HIV; failure to have sufficient erection (after prostaglandin E or Trimix injection); calcified plaque that would prevent proper injection; isolated hourglass deformity without curvature; plaque causing curvature located proximal to the base of the penis; treatment or plans to undergo treatment for PD (e.g., surgery, oral/topical /intralesional agents within 3 months, extracorporeal shock wave therapy within 6 months, use of mechanical devices within 2 weeks); ED unresponsive to PDE inhibitors; compromised penile hemodynamics determined to be clinically significant; uncontrolled HTN, known recent history of stroke, bleeding, or other significant medical condition; investigational drug treatment including CCH within 30 days; allergy to collagenase; received anticoagulant medication (excluding daily ASA ≤165mg or OTC NSAID ≤ 8000mg) 7 days before each dose of study drug; previous CCH for PD | Pts. stratified according to degree of curvature (30-60 and 61-90)Randomized 2:1 CCH:PBOCCH 0.58mg (n=551)PBO (n=281)Each treatment cycle included 2 injections with an interval of 24-72 hours between injections.  Approximately 24-72 hours after the 2nd injection, patients underwent penile plaque modeling (using plaque as fulcrum point, investigator applied firm steady pressure to elongate and stretch the penis. Penis was held in this position for 30 seconds. Procedure was repeated 3 times). Pts. were instructed to perform standardized home penile modeling 3 times daily using similar procedure during the 6-week period between each treatment cycle.The treatment cycle was repeated after 6 weeks for up to 4 treatment cycles. After the 1st treatment cycle, subsequent cycles were not administered if curvature abnormality was reduced to <15° or further tx was not clinically indicated | Values for CCH and PBO respectively**Age (years):** 57.6±8.5; 57.9±8.3**Race white (%):** 95.8; 97.2**Family history of PD*** Yes (%): 4.7; 5.0
* No (%): 95.3; 95
* Unknown (n): 145; 79

**PD history (years):** 4.1±4.1; 4.1±4.8**Penile curvature (degrees):** 50.1±14.4; 49.3±14**Penile curvature deformity 30-60 degrees (%):** 77.1; 77.6**Penile curvature deformity >60 degrees (%):** 22.9; 22.4**PDQ bother domain score:** 7.5±3.5; 7.8±3.7**PDQ symptoms domain score:** 10.8±5.0; 10.6±5.1**Penile trauma (%):** 23.4; 25.3**History of ED (%):** 47.5; 53.7 |

|  |  |  |
| --- | --- | --- |
|  | **CCH** | **PBO** |
| Received 8 injections (%) | 78.8 | 87.9 |
| Penile curvature at 52 weeks (degrees) | 33.1±16.8\* | 40±16.2 |
| Change in curvature (%) | -34\* | -18.2 |
| Δ PDQ bother domain scoreⱡ | -2.8±3.8\* | -1.8±3.5 |
| Global responders (%)§ | 60.8\* | 29.5 |
| Δ PDQ symptoms domain score\*\* | -2.9±5.0\* | -1.3±4.6 |
| IIEF overall satisfactionᴽ |  |  |
| Composite responder (%)¶ | 46.6\* | 28 |
| Δ penile plaque consistency ᵻ | -0.8±1.0\* | -0.5±0.9 |
| Penile length (cm) | 0.4±1.3 | 0.2±1.3 |
| PDQ penile pain score^ | -4.4±5.6 | -4.3±4.8 |

\*Significant vs. placeboⱡPDQ bother domain: composite score of concern about erection pain, erection appearance, impact on intercourse, frequency of intercourse (score range 0-16)§PD improved in small but important way, or modestly or much improved after treatment\*\*PDQ physical and psychological symptoms domain (6 questions; total possible score of 0-30)ᴽIIEF=international index of erectile function¶showing both ≥20% improvement in penile curvature and improvement of ≥1 in the symptom bother PDQ score or change from reporting no sexual activity at screening to reporting sexual activityᵻPlaque consistency scale: 5=hard, 4=firm throughout, 3=moderate firmness, 2=soft, 1=nonpalpable^subgroup of patients with pain score >4 at baseline (CCH n=164; PBO n=91) |