Drugs (2015) 75:1405–1412
DOI 10.1007/s40265-015-0441-7

ADIS DRUG EVALUATION

Collagenase Clostridium Histolyticum: A Review in Peyronie's Disease

Sohita Dhillon[1]

Published online: 23 July 2015

Abstract Collagenase Clostridium Histolyticum (CCH) (Xiaflex®, Xiapex®) intralesional injection is a mixture of class I (AUX-I) and class II (AUX-II) clostridial collagenases. It is indicated for the treatment of adult men with Peyronie's disease with a palpable plaque and curvature deformity of ≥30° at the start of therapy. This article reviews the efficacy and tolerability of CCH in this indication and briefly summarizes its pharmacology. CCH treatment significantly improved penile curvature deformity and reduced patient-reported bother associated with Peyronie's disease in the 52-week, double-blind, phase III IMPRESS I and II studies. Treatment benefit with CCH was also seen in 36-week, open-label studies, providing further support for its efficacy. CCH was generally well tolerated in patients with Peyronie's disease, with most treatment-related adverse events being of mild or moderate severity. Serious treatment-related adverse events (penile haematoma or corporal ruptures) were reported in <1 % of CCH recipients in clinical studies. Although further studies assessing the long-term effects of CCH intralesional injection are needed, current evidence indicates that this is a minimally invasive, effective and generally well tolerated treatment option for patients with Peyronie's disease.

Collagenase Clostridium Histolyticum in Peyronie's disease: a summary

A mixture of AUX-I and AUX-II clostridial collagenases with hydrolytic activity towards collagen

Disrupts collagen types I and III, the predominant collagen types in PD plaques

Improves penile curvature deformity and reduces patient-reported bother in Peyronie's disease patients

Penile haematoma, penile pain and penile swelling are the most common treatment-related adverse events

1 Introduction

Peyronie's disease (PD) is a fibrotic disorder characterized by penile plaque formation in the tunica albuginea, resulting in a variety of deformities, such as curvature, shortening, narrowing and hinge defect [1–3]. PD has a major impact on patients' sexual and psychological function [4], with almost half of the patients having relationship problems and clinically meaningful depression and 81 % of patients having emotional problems [5, 6]. While incidence rates of 3–10 % have been reported in the general population [7], its prevalence is likely to be higher, as patients may be embarrassed to discuss the condition or may avoid seeking medical advice if the symptoms are not disabling, resulting in under-reporting [1]. In addition, higher incidence rates of PD have been reported in some

The manuscript was reviewed by: ***W. J. G. Hellstrom***, Department of Urology, Tulane University School of Medicine, New Orleans, LA, USA; ***A. W. Pastuszak***, Scott Department of Urology, Baylor College of Medicine, Houston, TX, USA.

✉ Sohita Dhillon
demail@springer.com

[1] Springer, Private Bag 65901, Mairangi Bay, 0754 Auckland, New Zealand

patients subgroups, such as those with type 2 diabetes (8 %), patients who have had radical prostatectomy (16 %) and those who have both type 2 diabetes and erectile dysfunction (20 %) [8].

Treatment options for PD include pharmacological therapy, which is primarily indicated for patients with early-stage disease, and surgical treatment, focussed on patients with stable disease for ≥3 months [9]. Although several pharmacological treatment options are available (e.g. intralesional or topical verapamil, oral potassium para-aminobenzoate, intralesional interferon), varying degrees of success have been reported in clinical studies assessing these options [9]. Of these agents, only potassium para-aminobenzoate is approved for use in some countries in Europe [10], while none of the agents are approved for use in the USA. Collagenase Clostridium Histolyticum (CCH) (Xiaflex®, Xiapex®) intralesional injection is the first pharmacological treatment option approved for use in the USA and EU for patients with PD. It is indicated for the treatment of adult men with PD who have a palpable plaque and curvature deformity of ≥30° at the start of therapy [11, 12]. This article reviews the efficacy and tolerability of CCH in this indication and briefly summarizes its pharmacology.

2 Pharmacodynamic Properties of CCH

CCH consists of a mixture of AUX-I and AUX-II clostridial collagenases in a defined mass ratio [11, 12]. Collagenases are proteinases that hydrolyze collagen under physiological conditions [11, 12]. AUX-I and AUX-II are single polypeptide chains of ≈1000 amino acids and have a molecular weight of 114 and 113 KDa, respectively [11, 12]. They represent the two major collagenase classes (Class I and Class II) produced by the bacterium *Clostridium histolyticum* and have similar but complementary substrate specificity [12]. The ability of AUX-I and AUX-II to effectively cleave interstitial collagen at different sites and their preference for different conformations accounts for their complementary activity and broad hydrolytic activity towards collagen [12].

In vitro, CCH was selective for collagen types I and III (the predominant collagen types in PD plaques) and sparing of collagen type IV, which is present within connective tissues that surround arteries, large veins and nerves [13]. This selectivity results in the reduction of PD plaques without damage to surrounding elastic tissue, vascular smooth muscle or axon myelin sheaths [13–15]. Early clinical studies indicated the potential for CCH to be used for the treatment of patients with PD [16–19], with one phase IIb study demonstrating the benefit of penile modelling in conjunction with intralesional CCH [19]. In this study, patients who underwent physician modelling had significant ($p < 0.05$) improvement in penile curvature and PD symptom bother scores with CCH relative to placebo, but no significant between-group difference was seen in patients without modelling [19]. The efficacy of CCH in large phase III studies is discussed in Sect. 5.

3 Pharmacokinetic Properties of CCH

After administration of two intralesional CCH 0.58 mg injections (separated by 24 h) into the penile plaque in 19 patients with PD, plasma concentrations of AUX-I and AUX-II were minimal and short-lived in patients with quantifiable levels of AUX-I and AUX-II (82 and 40 % of patients, respectively) [12, 20]. The maximum individual plasma concentrations of AUX-I and AUX-II were <29 and <71 ng/mL, respectively [11, 12, 20], which were seen within ≈10 min of the injection [11]. Plasma levels in all patients were below the limits of quantification within 30 min of administration [11, 12, 20]. No evidence of accumulation was seen following two CCH injections administered 24 h apart [11, 12]. In addition, no patient had quantifiable plasma concentrations of AUX-I and AUX-II 15 min after modelling of plaque on day 3 (i.e. 24 h after the second injection on day 2) [11, 12, 20]. Clinical studies of CCH have not shown any evidence of systemic toxicity when the agent was administered as a localized injection into the Peyronie's plaque [12].

No metabolism studies have been performed, as CCH is not a substrate for cytochrome P450 enzymes or other metabolizing enzyme pathways and because no active metabolites are expected [12]. No studies have been conducted to assess the elimination of CCH; only minimal and short-lived systemic exposure was seen in patients with PD after administration a single injection of CCH [12].

No dosage adjustment of CCH is needed in special patient populations, including the elderly [11, 12], renally or hepatically impaired patients or on the basis of gender or race [12]. The use of CCH in paediatric patients has not been evaluated [11, 12].

4 Potential Drug Interactions of CCH

No formal drug interaction studies of CCH have been undertaken [12]. In vitro data showed that tetracycline and anthracycline/anthraquinolone antibiotics and derivatives of anthraquinone inhibit matrix metalloproteinase-mediated collagen degradation; therefore, the use of CCH in patients who have received tetracycline antibiotics within 14 days prior to a CCH injection is not recommended [12]. Owing to the risk of bleeding, caution is advised when CCH is used in patients with coagulation disorders or in

those taking anticoagulants [12]; its use is not recommended [12] or it should be avoided [11] in patients who have received anticoagulants [with the exception of low-dose (≤150 mg/day) aspirin] within 7 days prior to receiving a CCH injection. No clinically significant effect on the incidence of adverse events is seen when CCH is used concomitantly with phosphodiesterase type 5 inhibitors [12].

5 Therapeutic Efficacy of CCH

5.1 Placebo-Controlled Studies

The efficacy of CCH intralesional injections in men with PD was assessed in two large, identically designed 52-week, randomized, double-blind, placebo-controlled, phase III clinical studies, IMPRESS I ($n = 417$) and IMPRESS II ($n = 415$) [21]. Men aged ≥18 years who had PD for ≥12 months, with a penile curvature of ≥30° in the dorsal, lateral or dorsal/lateral plane during stable disease were eligible for the studies; patients with a penile curvature of <30° or >90°, or with ventral curvature from any cause were excluded [21]. At baseline, across both studies, the mean age of the patients was 57.7 years, the mean duration of disease was 4.1 years, 49.6 % of patients had a history of erectile dysfunction, and 77.3 % of patients had a penile deformity of ≤60° [22].

Patients were stratified by the degree of the penile curvature abnormality (30°–60° or 61°–90°) and randomized (2:1) to receive CCH or placebo for ≤4 treatment cycles 6 weeks apart, followed by a non-treatment follow-up period during weeks 24–52 [21]. In each treatment cycle, patients were administered two injections of CCH (0.58 mg/injection) or placebo (10 mmol/L tris and 60 mmol/L sucrose) 24–72 h apart. Approximately 24–72 h after the second injection of each treatment cycle, a penile modelling procedure was performed on the patients at the study site. In addition, patients were instructed to perform penile modelling three times daily at home for 6 weeks after each treatment cycle. Subsequent treatment cycles were not administered if after the first cycle, treatment was not clinically indicated or if the penile curvature abnormality was reduced to <15° [21].

The coprimary efficacy endpoints were the percent improvement from baseline in penile curvature and the change from baseline in the PD symptom bother domain (see Table 1 for definitions) [21]. A post-hoc pooled analysis of the data from IMPRESS I and II was conducted to improve the statistical power for evaluating several secondary endpoints [21].

5.1.1 Primary Endpoints

In IMPRESS I and II, treatment with CCH significantly improved penile curvature abnormality in patients with PD, as indicated by an approximately twofold greater reduction in penile curvature at week 52 with CCH than with placebo (Table 1) [21]. A consistent improvement in penile curvature was seen over the course of the studies, with significantly ($p < 0.01$) greater reductions in mean curvature at weeks 24, 42 and 52 with CCH than with placebo, and treatment benefits apparent as early as after the first treatment cycle (mean curvature at week 6 was reduced almost twice as much with CCH) [23, 24]. Results of the pooled analysis supported the findings of the individual studies (Table 1), with a significantly greater mean change in curvature per patient with CCH than with placebo (−17.0° vs. −9.3°; $p < 0.0001$) [21]. CCH treatment also significantly reduced patient-reported bother associated with PD [as assessed by the Peyronie's disease questionnaire (PDQ) PD symptom bother domain score] at week 52 in the individual studies and the pooled analysis (Table 1) [21]. The PDQ, a 15-question survey composed of three domains (symptom bother, psychological and physical symptoms, and penile pain), was developed specifically to quantify the psychosocial impact of PD [25]. It has demonstrated acceptable internal consistency and construct validity [25] and was found to be highly responsive to change in men with PD [26].

5.1.2 Secondary Endpoints

At week 52, with the exception of CCH recipients having significantly ($p < 0.0001$) higher global response rates in IMPRESS I (66.2 vs. 29.1 %) and IMPRESS II (55.4 vs. 29.9 %), and composite response rates in IMPRESS I (50.6 vs. 25.4 %), there were no significant differences between the CCH and placebo groups for the secondary endpoints in the individual studies (see Table 2 for definitions) [21]. However, in the pooled analysis, significant ($p < 0.05$) benefit with CCH over placebo was seen for the global (60.8 vs. 29.5 %) and composite (46.6 vs. 28.0 %) response rates and the mean improvement from baseline in PDQ PD symptom score (−2.9 vs. −1.3; baseline ≈11), penile plaque consistency score (−0.8 vs. −0.5) and the International Index of Erectile Function overall satisfaction (IIEF) score (1.0 vs. 0.4; baseline 5.6). No significant between-group differences in penile length (mean change 0.4 vs. 0.2 cm; baseline ≈11 cm) and PDQ pain scores (mean change −4.4 vs. −4.3; baseline ≈9) were seen in the pooled analysis [21].

Table 1 Efficacy of Collagenase Clostridium Histolyticum intralesional injection in patients with Peyronie's disease in two identical randomized, double-blind, phase III trials and a post-hoc pooled analysis of these trials [21]

Study (no. of mITT pts)	Penile curvature[a] [degrees]		PDQ PD symptom bother domain total score[b]	
	Mean change at wk 52 (BL)	% change[c]	Mean change at wk 52[c] (BL)	% change
IMPRESS I				
CCH ($n = 199$)	31.0 (48.8)	−37.6**	4.2 (7.5)	−3.3*
PL ($n = 104$)	39.0 (49.0)	−21.3	5.4 (7.4)	−2.0
IMPRESS II				
CCH ($n = 202$)	35.1 (51.3)	−30.5**	5.0 (7.4)	−2.4*
PL ($n = 107$)	41.1 (49.6)	−15.2	6.5 (8.2)	−1.6
Pooled analysis				
CCH ($n = 401$)	33.1 (50.1)	−34.0***	4.6 (7.5)	−2.8**
PL ($n = 211$)	40.0 (49.3)	−18.2	6.0 (7.8)	−1.8

BL baseline, *CCH* Collagenase Clostridium Histolyticum, *mITT* modified intent-to-treat (pts with a penile curvature abnormality measurement and a PDQ response at BL and ≥1 subsequent time point), *PD* Peyronie's disease, *PDQ* PD questionnaire, *PL* placebo

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.0001$ vs. PL

[a] Defined as the distance from the corona to the maximum point of curvature after injecting prostaglandin E1 or trimix into a corpus cavernosum to induce erection

[b] PD symptom bother domain consisted of four scored items (erection pain, erection appearance, and the impact of PD on intercourse and on the frequency of intercourse; score range 0–16) and two yes/no questions that were not scored or counted as distinct items [22, 25]

[c] Coprimary endpoints

Table 2 Definition/descriptions of secondary endpoints in the IMPRESS I and II studies [21]

Endpoint	Definition/description
Composite response	≥20.0 % improvement in penile curvature plus an improvement in the PDQ PD bother score of ≥1, or a change from reporting no sexual activity at screening to reporting sexual activity
Global response	Global PDQ score of ≥1 (a small but important improvement, or moderate or much improvement in PD)
IIEF	Consists of five domains (erectile function, orgasmic function, sexual desire, intercourse satisfaction and overall satisfaction)
PDQ PD symptom score	Assessed by the PDQ psychological and physical symptom domain (6 items; score range 0–30)
PDQ penile pain domain score	Assessed in patients with a pain score of ≥4 at baseline (3 items; score range 0–30)
Penile plaque consistency	Flaccid penis primary plaque consistency [score range 5 (hard) to 1 (nonpalpable)]

IIEF International Index of Erectile Function, *PD* Peyronie's disease, *PDQ* PD questionnaire

5.1.3 Subgroup Analyses

The benefit of CCH therapy over placebo was seen in various subgroups of patients with PD in post hoc subgroup analyses of pooled data from IMPRESS I and II [27]. Patients were stratified according to baseline parameters: severity of penile curvature deformity [30°–60° ($n = 492$) and 61°–90° ($n = 120$)]; disease duration [1 to ≤2 ($n = 201$), >2 to ≤4 ($n = 212$) and >4 years ($n = 199$)]; degree of plaque calcification [no calcification ($n = 447$), noncontiguous stippling ($n = 103$) and contiguous calcification that did not interfere with the injection ($n = 62$)]; and erectile function IIEF score of 1–5 (no sexual activity; $n = 22$), 6–16 (low erectile function; $n = 106$) and ≥17 (high erectile function; $n = 480$)] [27].

At week 52, penile curvature deformity was significantly ($p < 0.01$) reduced with CCH relative to placebo regardless of the severity of penile curvature deformity at baseline [27]. Significant ($p < 0.0001$) reductions in this outcome with CCH were also seen in patients with disease duration of >2 to ≤4, and >4 years, in those with no calcification and in patients with high erectile function. In terms of PD symptom bother scores, significant ($p < 0.05$) reductions with CCH at week 52 were seen in patients with penile curvature deformity of 30°–60°, disease duration of >4 years, no calcification, and no sexual activity or high erectile function [27].

Another post hoc analysis showed that in CCH-treated subjects whose final penile curvature deformity was less than or equal to that of the lowest 50 % of penile curvature deformity at baseline (i.e. a penile curvature deformity of ≤45° at the end of the study; $n = 314$), CCH treatment was associated with clinically meaningful improvements in curvature deformity (i.e. >20 % mean reduction) and PD symptom bother score (i.e. >2 point mean reduction) relative to placebo [28]. Moreover, greater improvements in curvature deformity with CCH relative to placebo were associated with greater reductions in PD symptom bother scores (coefficient of correlation 0.30; $p < 0.0001$) [28].

5.2 Open-Label Studies

Results of two 36-week, open-label, phase III studies in patients with PD supported the findings of the randomized clinical trials; in both studies, CCH was administered as in the IMPRESS studies (Sect. 5.1), with patients receiving ≤4 treatment cycles 6 weeks apart and being followed up until week 36 [20, 29].

One study enrolled 347 men who were CCH-naïve, had received one CCH treatment cycle in a phase II pharmacokinetic study (NCT01430169) or had received placebo in an earlier phase II study [19]; of these patients, 238 were evaluable for efficacy [20]. Results showed that CCH recipients experienced clinically meaningful and statistically significant improvements from baseline to week 36 in penile curvature deformity (mean improvement 34.4 %; 95 % CI 31.2–37.6) and PD symptom bother score (mean improvement 3.3; 95 % CI 2.8–3.7) (coprimary endpoints) [20].

The other study enrolled 189 men who had previously received placebo in IMPRESS I and II [29]. CCH treatment in these patients was also associated with significant improvements from baseline to week 36 in penile curvature deformity (mean reduction 36.3 %; 95 % CI −41.6 to −30.9) and PD symptom bother score (mean reduction 2.4; 95 % CI −3.0 to −1.88) (coprimary endpoints) [29].

6 Tolerability of CCH

6.1 In IMPRESS I and II

CCH intralesional injections were generally well tolerated in patients with PD in the IMPRESS I and II studies [21]. The pooled safety population comprised 551 CCH and 281 placebo recipients, of which 78.8 and 87.9 % of patients, respectively, received the maximum number of treatment cycles (8 injections). Although the majority of CCH recipients experienced treatment-related adverse events (AEs) local to the penis and groin after ≤4 treatment cycles (84.2 vs. 36.3 % of placebo recipients), these were usually of mild or moderate severity and most (≈79.0 %) resolved without intervention within 14 days.

The most common (incidence >45 %) treatment-related AEs with CCH that occurred at a higher incidence than with placebo were penile ecchymosis (including haematoma) (80.0 vs. 26.0 %), penile swelling (55.0 vs. 3.2 %) and penile pain (45.4 vs. 9.3 %) [21]. Severe penile haematoma or severe injection-site haematoma were reported in 6 % of CCH and 0 % of placebo recipients [11], and a 'popping' noise or sensation in the penis (sometimes accompanied with detumescence, haematoma and/or pain) occurred in 13.2 and 0.3 % of patients in the respective groups [11, 12]. Serious treatment-related AEs were reported in six CCH recipients, including three corporal ruptures (all repaired surgically) and three penile haematomas (one repaired surgically, one resolved with aspiration and one resolved without intervention) [21]. Owing to the risk of corporal rupture or other serious penile injury after treatment with CCH (which may require surgical intervention), signs or symptoms reflecting serious injury to the penis should be evaluated promptly [11, 12].

There were no significant differences between the CCH and placebo groups for laboratory or vital signs [21]. As with other non-human protein medicinal products, patients receiving CCH may develop antibodies to the injected protein [12]. Of the 539 CCH recipients evaluated for immunogenicity, 75 and 53 % of patients had positive AUX-I and AUX-II anti-drug antibodies, respectively, after the first treatment cycle; by week 52, these antibodies were detected in 99 and 98 % of patients in the respective groups [21]. However, no systemic immunological events were reported in these patients [21].

6.2 Pooled Analysis

A pooled safety analysis of data from six clinical studies (three phase IIb and three phase III; $n = 1044$), including the IMPRESS I and II studies, also showed that CCH intralesional injections were generally well tolerated in patients with PD [30]. Treatment-related AEs occurred in 85.8 % of CCH recipients in this analysis, most (75.2 %) of which were of mild or moderate severity; 14.2 % of patients did not experience any such AEs. The most common (incidence >25 %) treatment-related AEs with CCH were penile haematoma (50.2 %), penile pain (33.5 %) and penile swelling (28.9 %). Severe treatment-related adverse events occurred in 10.6 % of CCH recipients, with severe penile haematoma reported in 39 (3.7 %) patients [30].

Nine (0.9 %) CCH recipients had serious treatment-related AEs (penile haematoma in five and corporal rupture in four patients), of which only four patients (0.4 %) required surgical intervention [30]. Two patients discontinued CCH treatment because of serious treatment-related

AEs (one patient each with penile haematoma and corporal rupture) and seven patients because of non-serious treatment-related AEs. In addition, nine (0.9 %) CCH recipients had combined AEs of penile ecchymosis or haematoma, sudden penile detumescence and/or a penile 'popping' sound or sensation in which corporal rupture could not be excluded; all these patients were managed non-surgically. No treatment-related deaths were reported in CCH recipients [30].

Although antibodies against AUX-I and AUX-II were detected in ≥95 % of CCH recipients after two treatment cycles (≤4 injections), data from phase III studies found no association between antibody titres and the incidence, duration or severity of the three most common AEs (penile haematoma, penile pain and penile swelling) or the four AEs possibly consistent with an immunologic event (pruritus, genital pruritus, injection-site pruritus, lymphadenopathy) [30]. There were no treatment-related severe Type 1 or Type 3 systemic hypersensitivity reactions with CCH therapy; three local rashes and three reports of mild local pruritus were considered drug-related and one patient discontinued treatment because of papular dermatitis considered probably drug-related [30].

7 Dosage and Administration of CCH

CCH injection is indicated for the treatment of adult men with PD with a palpable plaque and curvature deformity of ≥30° at the start of therapy [11, 12]. The recommended dose of CCH is 0.58 mg per injection administered into a Peyronie's plaque; if more than one plaque is present, only the plaque causing the curvature deformity should be injected. A treatment course consists of a maximum of four treatment cycles, where each treatment cycle consists of two CCH injections and one penile modelling procedure. The second CCH injection should be administered 1–3 days after the first injection and a penile modelling procedure performed 1–3 days after the second injection of each treatment cycle. The interval between treatment cycles should be ≈6 weeks. Subsequent treatment cycles should not be administered if the penile curvature abnormality is reduced to <15° after the first, second or third treatment cycle, or if it is determined that further treatment is not clinically indicated [11, 12].

CCH is contraindicated for the treatment of Peyronie's plaques that involve the penile urethra, due to potential risk to this structure [11, 12]. The US prescribing information also carries a boxed warning regarding the risk of corporal rupture or other serious penile injury with CCH [11]. It is recommended that patients wait ≥2 weeks after the second injection of a treatment cycle before resuming sexual activity, provided pain and swelling have subsided [11, 12]. Local prescribing information should be consulted for comprehensive information on dosage and administration, contraindications, warnings and precautions.

8 Current Status of CCH in Patients with Peyronie's Disease

CCH intralesional injection is the first pharmacological option approved in the USA and across the EU for the treatment of PD. CCH is mixture of AUX-I and AUX-II clostridial collagenases, which have selective hydrolytic activity towards collagen types I and III, resulting in the reduction of PD plaques without damage to surrounding elastic tissue, vascular smooth muscle or axon myelin sheaths (Sect. 2). Being administered as an intralesional injection, CCH is minimally invasive and has no significant systemic exposure (Sect. 3).

The clinical efficacy of CCH intralesional injection was demonstrated in the 52-week, double-blind IMPRESS I and II studies, which showed that CCH treatment significantly improved penile curvature deformity and reduced patient-reported bother associated with PD (Sect. 5.1.1). In addition, pooled data from the two studies suggested a treatment benefit in terms of several secondary endpoints and across various subgroups (Sect. 5.1). Treatment benefit was also seen in two 36-week open-label studies, which provided further support for its efficacy (Sect. 5.2). CCH was generally well tolerated in patients with PD, with penile haematoma, penile pain and penile swelling the most common treatment-related AEs, which were usually of mild or moderate severity (Sect. 6). There is also a risk, albeit low (incidence <1 % in clinical studies), of serious treatment-related adverse events (penile haematoma or corporal ruptures) with CCH.

In keeping with the results of the IMPRESS I and II studies, the recently published American Urology Association guidelines include CCH (in combination with modelling) as a treatment option for patients with PD [31]. CCH may be used for the reduction of penile curvature in patients who have stable PD with a penile curvature of >30° and <90° and intact erectile function (with or without the use of medications); the net benefit with CCH is moderate, given the modest size of curvature reduction and low risk of serious adverse events in the IMPRESS studies [31]. CCH should not be used in patients who meet the inclusion criteria for curvature and plaque, but whose primary concerns are penile pain and/or erectile dysfunction, as CCH does not treat these conditions [31]. Other pharmacological options that may be considered in patients with stable PD are intralesional interferon α-2b for curvature, plaque, and pain reduction (net benefit appears to be moderate) and intralesional verapamil for the treatment of

symptoms (net benefit is unclear) [31]. The current EU treatment guidelines, although published before the approval of CCH, also include CCH as a pharmacological treatment option for men with PD [9].

While the IMPRESS studies showed that CCH therapy improves penile deformity, some patients may have an unsatisfactory change in penile curvature and require surgical correction of the remaining deformity [32]. In order to determine if prior treatment with CCH has any negative impact on surgical straightening procedures, a small ($n = 7$) retrospective chart review examined the intraoperative and postsurgical outcomes of surgical correction of persistent penile curvature in CCH-experienced patients [32]. Results suggest that prior treatment with CCH does not limit a patient's subsequent surgical straightening treatment options [32]; however, further well-designed studies are needed to confirm these initial observations. Studies assessing the long-term effects of CCH therapy [2, 31], its use in patients with hourglass deformity, ventral curvature, calcified plaque or plaque located proximal to the base of the penis [31] and identifying predictors of optimal treatment success in subgroups of PD patients [27] would also be helpful.

To conclude, current evidence indicates that CCH intralesional injection is a minimally invasive, effective and generally well tolerated option for the treatment of patients with Peyronie's disease.

Data selection sources: Relevant medical literature (including published and unpublished data) on collagenase injection was identified by searching databases including MEDLINE (from 1946), PubMed (from 1946) and EMBASE (from 1996) [searches last updated 10 July 2015], bibliographies from published literature, clinical trial registries/databases and websites. Additional information was also requested from the company developing the drug.
Search terms: Collagenase injection, Xiapex, Xiaflex, Plaquase, AA-4500, PF-5076985, Peyronie.
Study selection: Studies in patients with Peyronie's disease who received collagenase injection. When available, large, well designed, comparative trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

Disclosure The preparation of this review was not supported by any external funding. During the peer review process, the manufacturer of the agent under review was offered an opportunity to comment on this article. Changes resulting from comments received were made by the author on the basis of scientific and editorial merit. Sohita Dhillon is a salaried employee of Adis/Springer.

References

1. Alwaal A, Hussein AA, Zaid UB, et al. Management of Peyronie's Disease after Collagenase (Xiaflex®). Curr Drug Targets. 2014;16(5):484–94.
2. Egui Rojo MA, Moncada Iribarren I, Carballido Rodriguez J, et al. Experience in the use of Collagenase Clostridium Histolyticum in the management of Peyronie's disease: current data and future prospects. Ther Adv Urol. 2014;6(5):192–7.
3. Moreland RB, Nehra A. Pathophysiology of Peyronie's disease. Int J Impot Res. 2002;14(5):406–10.
4. Rosen R, Catania J, Lue T, et al. Impact of Peyronie's disease on sexual and psychosocial functioning: qualitative findings in patients and controls. J Sex Med. 2008;5(8):1977–84.
5. Smith JF, Walsh TJ, Conti SL, et al. Risk factors for emotional and relationship problems in Peyronie's disease. J Sex Med. 2008;5(9):2179–84.
6. Nelson CJ, Diblasio C, Kendirci M, et al. The chronology of depression and distress in men with Peyronie's disease. J Sex Med. 2008;5(8):1985–90.
7. Sherer BA, Warrior K, Levine LA. 2013–2014 updates in Peyronie's disease management. Curr Urol Rep [Electronic Resource]. 2014;15(12):459.
8. Hussein AA, Alwaal A, Lue T. All about Peyronie's disease. Asian J Urol. 2015;2(2):70–8.
9. Hatzimouratidis K, Eardley I, Giuliano F, et al. EAU guidelines on penile curvature. Eur Urol. 2012;62(3):543–52.
10. Glenwood GmBH. Overview of Glenwood preparations. 2015. http://glenwood.de/. Accessed 26 June 2015.
11. Auxilium Pharmaceuticals Inc. Xiaflex (Collagenase Clostridium Histolyticum): US prescribing information. 2015. http://www.accessdata.fda.gov/. Accessed 29 June 2015.
12. European Medicines Agency. Xiapex (Collagenase Clostridium Histolyticum): summary of product sharacteristics. 2015. http://www.ema.europa.eu/. Accessed 29 June 2015.
13. Levine LA, Schmid TM, Emeigh Hart SG, et al. Collagenase Clostridium Histolyticum degrades type I and III collagen while sparing type IV collagen in vitro in Peyronie's plaque explants [abstract no. PD22-03 plus oral presentation]. In: American Urological Association Annual Meeting. 2014.
14. Gelbard MK, Walsh R, Kaufman JJ. Collagenase for Peyronie's disease experimental studies. Urol Res. 1982;10(3):135–40.
15. Del Carlo M, Cole AA, Emeigh Hart SG, et al. Comparative analaysis of collagen degradation in Peyronie's disease plaque and Dupuytren's contracture cord tissue injected with mixed collagenase subtypes [abstract no. 780]. J Urol. 2009;181(4 Suppl):279.
16. Gelbard MK, Lindner A, Kaufman JJ. The use of collagenase in the treatment of Peyronie's disease. J Urol. 1985;134(2):280–3.
17. Gelbard MK, James K, Riach P, et al. Collagenase versus placebo in the treatment of Peyronie's disease: a double-blind study. J Urol. 1993;149(1):56–8.
18. Jordan GH. The use of intralesional Clostridial collagenase injection therapy for Peyronie's disease: a prospective, single-center, non-placebo-controlled study. J Sex Med. 2008;5(1):180–7.
19. Gelbard M, Lipshultz LI, Tursi J, et al. Phase 2b study of the clinical efficacy and safety of Collagenase Clostridium Histolyticum in patients with Peyronie disease. J Urol. 2012;187(6):2268–74.
20. Levine LA, Cuzin B, Mark S, et al. Clinical safety and effectiveness of Collagenase Clostridium Histolyticum injection in patients with Peyronie's disease: a phase 3 open-label study. J Sex Med. 2015;12(1):248–58.
21. Gelbard M, Goldstein I, Hellstrom WJ, et al. Clinical efficacy, safety and tolerability of Collagenase Clostridium Histolyticum for the treatment of Peyronie disease in 2 large double-blind, randomized, placebo controlled phase 3 studies. J Urol. 2013;190(1):199–207.
22. Gelbard M, Hellstrom WJ, McMahon CG, et al. Baseline characteristics from an ongoing phase 3 study of Collagenase

Clostridium Histolyticum in patients with Peyronie's disease. J Sex Med. 2013;10(11):2822–31.
23. McMahon C, Auerbach S, Liu G, et al. Curvature deformity and symptom bother improvement over time in patients with Peyronie's disease treated with Collagenase Clostridium Histolyticum [abstract no. 1661]. In: 108th Annual Meeting of the American Urological Association. 2013.
24. European Medicines Agency. Assessment report (Xiapex). 2014. http://www.ema.europa.eu/. Accessed 26 June 2015.
25. Hellstrom WJ, Feldman R, Rosen RC, et al. Bother and distress associated with Peyronie's disease: validation of the Peyronie's disease questionnaire. J Urol. 2013;190(2):627–34.
26. Coyne KS, Currie BM, Thompson CL, et al. Responsiveness of the Peyronie's Disease Questionnaire (PDQ). J Sex Med. 2015;12(4):1072–9.
27. Lipshultz LI, Goldstein I, Seftel AD, et al. Clinical efficacy of Collagenase Clostridium Histolyticum in the treatment of Peyronie's disease by subgroups: results from two large, double-blind, randomized, placebo-controlled, phase 3 studies. BJU Int. 2015. doi:10.1111/bju.13096.
28. Lipshultz LI, Sadeghi-Nejad H, Mills J, et al. Peyronie's disease symptom bother reduction is related to penile curvature improvement in response to treatment with Collagenase Clostridium Histolyticum: results from two large double-blind, randomized, placebo-controlled phase 3 studies [abstract no. 075]. In: 20th Annual Fall Scientific Meeting of SMSNA. 2014.
29. Goldstein I, Knoll D, Lipshultz LI, et al. Changes in the effects of Peyronie's disease after treatment with Collagenase Clostridium Histolyticum according to men with Peyronie's disease and their female sexual partners [abstract no. 064]. In: 20th Annual Fall Scientific Meeting of SMSNA. 2014.
30. Carson CC, Sadeghi-Nejad H, Tursi JP, et al. Analysis of the clinical safety of intralesional injection of Collagenase Clostridium Histolyticum for adults with Peyronie's disease. BJU Int. 2015. doi:10.1111/bju.13120.
31. American Urological Association. Peyronie's disease: AUA guideline. 2015. https://www.auanet.org/education/guidelines/peyronies-disease.cfm. Accessed 26 June 2015.
32. Levine LA, Larsen SM. Surgical correction of persistent Peyronie's disease following collagenase clostridium histolyticum treatment. J Sex Med. 2015;12(1):259–64.