Medicines Optimisation Programme Board (MOPB)

Drug	Collagenase clostridium histolyticum
Indication	Peyronie's disease
Decision	Collagenase clostridium histolyticum is not routinely commissioned for the treatment of Peyronie's disease. Unless the condition interferes with inter-course it is considered predominantly to be a cosmetic issue and is therefore low priority. Treatment with collagenase or surgery will be considered on a case by case basis in patients where: • Conservative treatments have been tried and failed AND • The disease has stabilized AND • The disease is so significant that intercourse is not possible.
Date	31 Jan 2019
Evidence	See references below

Rationale for recommendation

Peyronie's disease

Definition

This is a benign penile condition characterized by curvature of the penile shaft secondary to the formation of fibrous tissue plaques within the tunica albuginea.

Background

This review summaries current evidence for the treatment of Peyronie's Disease. The review has been prompted by two reviews into evidence based treatment from the London Medicines Evaluation Network (LMEN) In July 2015 and the Bedfordshire and Hertfordshire Priorities Forum paper in September 2018.

Peyronie's disease (PD) is caused by excess scar formation in the penis, which may cause penile pain, shortening and curvature. It is often accompanied by erectile dysfunction, and can result in progressive and severe impairment of penetrative intercourse.

PD most commonly affects men in the sixth decade of life1, with men being typically affected between 55-60 years 2.The pathophysiology is poorly understood but minor trauma, genetic predisposition and risk factors such as poor circulation likely play a role.

The course of the disorder is divided into active inflammatory and chronic stable phases. Oral therapy is usually of limited efficacy, while penile traction may only be beneficial in motivated patients.

Intralesional injections of collagenase were recently introduced as a non-surgical measure to decrease penile curvature . Surgery remains the most effective treatment for Peyronie's disease. Surgical options are considered for patients with severe deformity usually with a curvature greater than 60 degrees that's prevents intercourse 4.

Non-Surgical treatment options

Numerous systemic drugs have been evaluated in the treatment of PD including procarbazine, vitamin E, propionyl-L-carnitine, acetyl-L-carnitine, tamoxifen, omega-3 fatty acids, interferon-α2a (IFNα2a), interferon-α2b (IFNα2b), pentoxifylline, L-arginine, sildenafil, colchicine, coenzyme Q10, and potassium paraaminobenzoate (POTABA). Most of the above have little proven efficacy 2.

Extracorporeal shockwave therapy (ESWT) has been evaluated in numerous studies that have not shown a benefit this is reflected in current NICE guidelines not supporting its use 3.

Collagenase clostridium histolyticum (Xiapex, Swedish Orphan Biovitrum AB) or CCH is a purified form of two collagenase enzymes which help to digest the penile plaque when used as a intralesional treatment, these enzymes manifest their effects through hydrolysis of types I and III collagen fibres. The European medicines agency (EMA) granted a licence extension in February 2015 having been previously licensed for Dupuytren's contracture 4

Evidence base

Key points of the London Medicines Evaluation Network (LMEN) review July 2015 4-5.

Two phase III studies IMPRESS 1 and IMPRESS 2 (Investigation for Maximal Peyronie's Reduction Efficacy and Safety Studies)

- Multicentre, randomised, double-blind, and placebo controlled trials. A total of 832 men were enrolled with an average penile curvature of 50 degrees.

- Inclusion criteria for the IMPRESS trial included stable disease, dorsal curvature between 30 and 90 degrees, and intact erectile function with or without use of phosphodiesterase 5 inhibitors

- These studies demonstrate significantly greater improvement in penile curvature and PD symptom bother score in the treatment arm compared to placebo, with effects on pain and erectile function similar to placebo

- Participants were given up to four treatment cycles of CCH or placebo and were then followed for 52 weeks. Overall, of 551 treated men with CCH 60.8% were global responders compared with 29.5% in the placebo arm.

- An average improvement of 34% in penile curvature, equivalent to −17.0±14.8° of curvature, was observed in the treatment arm, in comparison with 18% (−9.3±13.6°) in the placebo arm ($p < 0.0001$)

A phase III open label study 6.

- 347 men enrolled with a baseline penile curvature of 30° to 60° (mean 53°). The participants received upto 4 cycles of CCH with penile modelling at home. The mean penile curvature decreased by 18.3° (+/- 14.02°), a statistically significant improvement. The symptom bother score had reduced by 3.3 points at week 36.

PIIb study 7

- A randomised, double-blind, placebo controlled PIIb study was carried out in 147 men with PD.

- The men were randomised (3:1) to one of four possible groups; penile modelling plus either intralesional CCH (n=54), placebo (n=20), intralesional CCH(n=57) or placebo without penile modelling (n=16). Up to six injections of CCH 0.58mg or placebo (as 3 cycles of 2 injections given 6 weeks apart) were injected.

- In the non-modelled group, mean penile curvature was reduced at 36 weeks by -15° (+/- 14.0°) in the CCH group vs. -13.0° (+/- 10.7°) in the placebo group (p=0.9). In the modelled group, mean penile curvature was reduced at 36 weeks by -17.5° (+/- 15.3°) in the CCH group vs. + 0.6° (+/- 13.2°) in the placebo group (p<0.001). Therefore, only CCH plus modelling significantly reduced mean penile curvature compared to placebo at 36 weeks.

Further literature identified by the Priorities forum between 2015 and January 2018 8

Summary below

- 2 small non randomised studies assessing efficacy the first study 9, looked at CCH treatment in 49 men in a single centre. mean pre-treatment penile curvature was 49.3 degrees. Curvature was reduced by 15.4 degrees (32.4%, $P < .01$). follow up was at 183 days after 3 cycles of treatment. Subjectively, there was an improvement in the ability to

perform intercourse (29.1% improvement, *P* < .01) and bother symptoms (mean decrease 43.2%, *P* < .01), Five bleeding events (10.2%) were noted.

- The second post release study looked at 69 patients 10. 88% reported subjective improvement after 4 injections. A mean 23-degree curvature improvement was also found (38%, p <0.0001). Seven patients (10%) experienced penile hematomas. 14 patients reported that CCH injections negated the need for surgery whilst 3 had surgery after completing treatment. A large loss to follow up reported at 6 months.

- 3 studies 11-13 looking at patient satisfaction showed improvement post treatment using a patient questionnaires.

- 3 studies 14-16 assessed adverse outcomes. Study 13 looked at pooled data from 6 trials and found 85.8% of 1 044 pooled patients reported at least one treatment-related adverse event. The most frequently reported (≥25.0% of patients) included penile haematoma , penile pain, and penile swelling. Most patients (75.2%) had mild- or moderate-severity treatment-related Adverse events, and 14.2% had no treatment-related adverse outcomes. Nine patients (0.9%) had serious adverse affects which included five with penile haematoma and four with corporal rupture

Update literature from January 2018 to December 2018.

No Randomized control trials identified. One study 17 with 57 patients assessed the Efficacy of collagenase clostridium histolyticum (CCH) and surgical interventions tunical plication [TP] and partial plaque excision and grafting [PEG].

CCH was administered to 18 patients, TP performed in 14, and PEG in 25. The median follow-up for the whole cohort was 12 months (6-28). Mean changes in curvature after treatment were 23.3° (34.4%) for CCH, 72.0° (92.2%) for TP, and 71.8 ° (94.9%) for PEG, *P*<.001. Mean changes in International Index of Erectile Function-5 scores were +5.7 for CCH, +4.9 for TP, and +2.2 for PEG, *P* = .395.

Conclusions

The best evidence for the efficacy of CCH comes from the IMPRESS trials. They demonstrated a modest reduction in penile curvature and good patient satisfaction when compared to placebo. It is also clear that modeling post procedure is key which could account for the reduction in curvature in the placebo arm of the trial. Limitations include the strict exclusion criteria which limit generalizability . Only One trial compares surgery with CCH it is however limited by its small size and lack of randomization. It does however show a larger curvature correction with surgery which is supported by previously conducted trials assessing surgery.

Current NICE position

Following a consultation exercise and scoping workshop in 2015, NICE decided that an appraisal of collagenase clostridium histolyticum and potassium para-aminobenzoate for treating Peyronie's disease was not appropriate. This was due to the small population size (no more than 500 patients likely to be eligible) and individualized approach to patient care (because of the heterogeneous nature of the condition).20

Surgical treatment

Surgery is indicated in men whose penile curvature is stable but exceeds 60 degrees 4.Currently, surgical treatment alternatives are reconstructive surgery by either lengthening the concave side (incision and grafting) or shortening the convex side (Nesbit procedure or plication) of the penis, and implantation of penile prosthesis with or without incision of the plaque.

A evidence review by the Canadian urological association 19, has shown curvature correction rates range from 42–100% with plication procedures and overall satisfaction ranges from 68–100%, with primary satisfaction determinants being straightening and improved sexual performance; conversely, dissatisfaction

correlates to postoperative penile shortening. Complete deformity correction rates range from 50–98% with grafting techniques and the satisfaction rates are highly variable from 35–51%.

Cost analysis

The LEMN estimates one cycle of treatment which is 2 injections is approximately £13004. The cost for 4 cycles is estimated at £5,200.

The LEMN estimated the cost at 550,000-2,200,000 per 100,000 people depending on the number of treatment cycles. This does not include costs associated with physician time, anaesthesia, and dressings.

In East and North Hertfordshire 8 a total of 11 surgical procedures (including plication of corpora of penis, graft to penis, and implantation of prosthesis) were carried out in 2016/17 costing a total of £30,095. The most common procedure was plication at £2,363 per procedure.

West Essex Data

No requests have been made for CCH treatment

3 surgical procedures carried out in 2017/2018 at a total cost of £5,606.

Recommendation

Conservative measures for treating PD should be trialed initially along with counseling regarding the condition.

CCH is the only medical treatment licensed by the EMA primarily based on the IMPRESS trials which showed a modest reduction in penile curvature and good patient satisfaction. There however remains lack of good evidence with a comparator treatment such as surgery.

I recommend that CCH is not routinely funded and requests are assessed on a individual bases when there is severe disease and difficulty with intercourse and surgical treatment is contraindicated. Surgical treatment should be reserved for patients not able to have sexual intercourse due to peyronie's disease.

Extracorporeal shockwave therapy is not recommended due to a lack of efficacy as supported by NICE guidelines 3.

References

1. Mulhall JP, Schiff J, Guhring P. An analysis of the natural history of Peyronie’s disease. The Journal of urology. 2006; 175(6):2115–2118

2. European Association of UrologistsK Hatzimouratidis (Chair), I. Eardley, F. Giuliano, I. Moncada, A. Salonia. *Guidelines on Penile Curvature* Eur Urol 2012 Sep;62(3):543-52.

3. NICE. Extracorporeal shockwave therapy for Peyronie's disease. 2003. Interventional procedure guidance 29. https://www.nice.org.uk/guidance/ipg29/chapter/5-About-this-guidance

4. London Medicines Evaluation Network. Collagenase Clostridium histolyticum (XiapexTM) for Peyronie’s disease – July 2015 https://www.sps.nhs.uk/wp-content/uploads/2015/08/LMEN_Xiapex_Peyronies_July15.pdf

5. Gelbard M, Goldstein I, Hellstrom W.J.G et al. Clinical efficacy, safety and tolerability of collagenase clostridium histolyticum for the treatment of Peyronies disease in 2 large double-blind, randomized, placebo controlled phase 3 studies. J Urol 2013; 190(1):199-207.

6. 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. The journal of sexual medicine. 2015; 12(1):248–258.

7. Levine LA, Cuzin B, Stephen M et al. Clinical safety and effectiveness of collagenase clostridium histolyticum injection in patients with Peyronie's disease; a phase 3 open label study. The Journal of Sexual Medicine 2015; 12(1):248-258.

8. Bedfordshire and Hertfordshire Priorities Forum statement Number: 98 Subject: Peyronie's Disease September 2018

9. Yang, Kevin K. et al. Peyronie's Disease and Injectable Collagenase Clostridium histolyticum: Safety, Efficacy, and Improvements in Subjective Symptoms. *Urology* Volume 94 , 143 - 147 https://www.ncbi.nlm.nih.gov/pubmed/27211926

10. Ziegelmann M, Viers B, McAlvany K et al. Resoration ofPEnile Function and Paitnet Satisfaction with Intralesional Collagenase Clostridium Histolytic Injection for Peyronie's Disease. Journal of Urology. 195(4):1051-1056

11. 8.Anaissie, J., Yafi, F. A., Traore, E. J., Sikka, S. C. and Hellstrom, W. J. G. (2017), Survey of patient and partner satisfaction following collagenase *Clostridium histolyticum* treatment for Peyronie's disease. Andrology, 5: 274–277. doi:10.1111/andr.12302

12. 9.Coyne KS, Currie BM, Thompson CL, and Smith TM. Responsiveness of the Peyronie's Disease Questionnaire (PDQ). J Sex Med 2015;12:1072–1079.

13. 10.Thoma, C. CCH injections reader effective by men with Peyronie's disease. Nature Reviews Urology 2015;12:654 https://www.ncbi.nlm.nih.gov/pubmed/26526755

14. 11.Abdel Raheem, A., Capece, M., Kalejaiye, O., Abdel-Raheem, T., Falcone, M., Johnson, M., Ralph, O. G., Garaffa, G., Christopher, A. N. and Ralph, D. J. (2017), Safety and effectiveness of collagenase clostridium histolyticum in the treatment of Peyronie's disease using a new modified shortened protocol. BJU Int, 120: 717–723. doi:10.1111/bju.13932

15. Carson, C. C., Sadeghi-Nejad, H., Tursi, J. P., Smith, T. M., Kaufman, G. J., Gilbert, K. and Honig, S. C. (2015), Analysis of the clinical safety of intralesional injection of collagenase *Clostridium histolyticum* (CCH) for adults with Peyronie's disease (PD). BJU Int, 116: 815–822. doi:10.1111/bju.13120

16. 13.Yafi, Faysal A. et al. Results of SMSNA Survey Regarding Complications Following Intralesional Injection Therapy With Collagenase Clostridium Histolyticum for Peyronie's Disease The Journal of Sexual Medicine , Volume 13 , Issue 4 , 684 - 689

17. Yafi,Faysal A.et al Multi-institutional Prospective Analysis of Intralesional Injection of Collagenase Clostridium Histolyticum, Tunical Plication, and Partial Plaque Excision and Grafting for the Management of Peyronie's Disease Urology , Volume 120 , 138 - 142

18. Surgical Treatment of Peyronie's Disease: A Critical Analysis Kadioglu, Ates et al. European Urology , Volume 50 , Issue 2 , 235 - 248

19. 16. Nehra, Ajay et al. "Peyronie's Disease: AUA Guideline" *Journal of urology* vol. 194,3 (2015): 745-53

20. National Institute for Health and Care Excellence.: https://www.nice.org.uk/Media/Default/About/what-wedo/NICE-guidance/NICE-technology-appraisals/Block-scoping-reports/Batch-43-block-scoping-report-noCIC.pdf