# AWMSG Secretariat Assessment Report – Advice no. 1711
# Collagenase *Clostridium histolyticum* (Xiapex®▼) 0.9 mg powder and solvent for solution for injection

This assessment report is based on evidence submitted by Pfizer Ltd on 7 June 2011.

## 1.0 PRODUCT DETAILS

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| **Licensed indication under consideration** | Collagenase *Clostridium histolyticum* (Xiapex®▼) is indicated for the treatment of Dupuytren's contracture in adult patients with a palpable cord[1]. |
| **Restrictions to submission** | The company have indicated that they wish to restrict their submission to the use of collagenase *Clostridium histolyticum* for the treatment of Dupuytren's contracture as an alternative to fasciectomy in a subset of adult patients with a total of two or less affected joints per hand, using up to three injections per cord, with no more than six injections per patient[2]. |
| **Dosing** | The recommended dose is 0.58 mg per injection into a palpable Dupuytren's cord. The volume to be administered into the Dupuytren's cord differs depending on the type of joint being treated[1].<br><br>Approximately 24 hours after injection, a finger extension procedure may be performed to facilitate cord disruption. Injections and finger extension procedures may be administered up to three times per cord at approximately four-week intervals. Only one cord must be treated at a time, with a maximum of three injections per cord[1].<br><br>Refer to the Summary of Product Characteristics (SPC) for further information regarding dosing for different joints[1]. |
| **Marketing authorisation date** | 28 February 2011[1,2]. |

## 2.0 DECISION CONTEXT

### 2.1 Background

Dupuytren's disease is a condition characterised by fibrosis of the ligaments that anchor skin to the palmar fascia, resulting in the formation of nodules and eventually collagenous cords[3–5]. Over time, these cords thicken and contract, drawing the affected fingers, commonly the ring and little fingers, into flexion[4–6]; this is classified as Dupuytren's contracture. Dupuytren's disease typically affects the elderly and is more common in men than in women[7,8]. In addition, men typically present with earlier onset (mean age of 55 years, compared with mean age in women of 65 years) and more severe disease[7,8]. It is rarely painful, but contracture can significantly limit hand function[2,8] and therefore the patient's daily activities. Dupuytren's disease occurs in all racial and ethnic groups, but incidence is highest in people of Northern European descent[9,10]. An epidemiology report published in 1999 estimated that Dupuytren's disease affects approximately 2 million people in the UK[7]. The mean incidence of

Dupuytren's contracture in the UK is estimated at 33 cases per 100,000 residents/year[11,12].

To determine the best course of action for Dupuytren's patients, the rate of disease progression and impact on daily activities must be considered on a case-by-case basis[13]. Most people with early Dupuytren's disease (presence of nodules with no contracture) do not require treatment, and approximately 10% of cases regress with no intervention[4]. For patients with contracture, the only effective treatment, until recently, has been surgery. Physical therapy, radiotherapy and splinting have demonstrated inconclusive effects on the progression of the disease[8,13,14]. A 1989–1990 study of Dupuytren's patients calculated an incidence of hospital referral of 32.5/100,000/year for Dupuytren's contracture, of which 20.5/100,000/year (63%) undergo surgery[15]. Despite surgery, recurrence is common (up to 65%), especially in aggressive disease[4,8,16,17].

Collagenase *Clostridium histolyticum* (CCH), a combination of type I (AUX-1) and type II (AUX-II) clostridial collagenases, was licensed in February 2011 for the treatment of Dupuytren's contracture in adult patients with a palpable cord[1]. The injection of these complementary collagenases directly into the cord results in cleavage of the built-up collagen, which helps straighten the finger[1]. The company stated that they have restricted their submission in order to maximise efficiency and reflect clinical practice, where CCH would likely be used in patients with a small number of affected joints; they suggest that CCH should be used as an alternative to fasciectomy in adults with moderate to severe Dupuytren's contracture (according to British Society for Surgery of the Hand [BSSH] guidelines[13]), with two or less affected joints per hand, using up to three injections per cord, with no more than six injections per patient[2].

### 2.2 Comparators

The Welsh Medicines Partnership (WMP) is of the opinion that surgery is the most appropriate comparator. The surgical procedures available for sufferers of Dupuytren's contracture are:

- fasciectomy (partial, limited, palmar or digital),
- fasciotomy (including percutaneous needle fasciotomy [PNF]),
- dermofasciectomy,
- amputation[3,8].

The company used fasciectomy as the comparator in their submission as this is the predominant procedure for the treatment of Dupuytren's contracture in England[3].

### 2.3 Guidance and related advice

- BSSH Evidence for Surgical Treatment 1 (BEST 1): Dupuytren's Disease[13]. These guidelines recommend PNF, collagenase or limited fasciectomy for moderate Dupuytren's disease (MP joint contracture 30–60 degrees or PIP joint contracture < 30 degrees), and limited or dermofasciectomy for severe disease (MP joint contracture > 60 degrees or PIP joint contracture > 30 degrees).
- National Institute for Health and Clinical Excellence (NICE). Interventional procedures guidance 043: Needle fasciotomy for Dupuytren's contracture (2004)[18].

## 3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

### 3.1 Clinical effectiveness evidence

The company submission provided detailed information for two prospective, multi-centre, double-blind, randomised, placebo-controlled phase III clinical trials which they consider pivotal: AUX-CC-857/858 (CORD I) and AUX-CC-859 (CORD II)[2]. The design of each study was identical. Dupuytren's disease patients with fixed-flexion contractures of at least 20 degrees in the MP or PIP joint in at least one finger (excluding the thumb) were included. Patients were excluded if they had contracture > 100 degrees for the MP joint or > 80 degrees for the PIP joint. Adult patients (≥ 18 years) were randomised 2:1 to CCH or placebo, and stratified according to joint type and severity of baseline joint contracture (≤ 50 degrees or > 50 degrees for MP joint and ≤ 40 degrees or > 40 degrees for PIP joint). Patients received an injection of CCH (0.58 mg) or placebo into a single (primary) cord, with finger extension exercises from 24 hours after the injection and follow-up at 1, 7 and 30 days. The primary endpoint was a reduction in primary joint contracture to ≤ 5 degrees of full extension 30 days after the last injection[2,5,19]. Secondary objectives were the evaluation of the same outcome in multiple joints and recurrence (defined as a ≥ 20 degree increase in contracture at any time during follow-up). Each patient could receive up to three injections during the 90-day double-blind study period. The primary cord could receive three treatment cycles; however, if the primary endpoint was met after one or two cycles, a second cord could be treated. Each injection was separated by approximately 30 days, as described in the SPC. After the 90-day period, patients were able to enter nine-month open-label studies in which they could receive up to five additional CCH injections. Statistical analysis of both trials was performed for the intent-to-treat (ITT) populations[2].

#### 3.1.1 CORD I

A total of 308 adult patients were randomised 2:1 to CCH (n = 204) or placebo (n = 104)[2,5]. Two subjects were excluded from the ITT populations (modified ITT), one from each group. The primary endpoint was met in 130/203 (64%) primary cords injected with CCH compared with 7/103 (6.8%) primary cords injected with placebo ($p < 0.001$). When results were analysed by joint type, 102/133 (76.7%) versus 5/69 (7.2%) MP joints ($p < 0.001$) and 28/70 (40%) versus 2/34 (5.9%) PIP joints ($p < 0.001$) treated with CCH versus placebo, respectively, met the primary endpoint. The median time to reach the primary endpoint in the CCH arm was 56 days. After the last injection in the double-blind or open-label phase, the primary endpoint was met in 264/523 (50.5%) cords treated with CCH (66.6% of MP joints and 29% of PIP joints). A total of 12/264 (4.5%) cords treated with CCH in CORD I had recurrent contracture (3 MP, 9 PIP)[2].

#### 3.1.2 CORD II

A total of 66 adult patients were randomised 2:1 to CCH (n = 45) or placebo (n = 21)[2,19]. The primary endpoint was met in significantly more primary cords injected with CCH than with placebo: 20/45 (44.4%) versus 1/21 (4.8%) ($p < 0.001$). When results were analysed by joint type, significantly more MP joints reached the primary endpoint when treated with CCH than placebo (13/20 [65%] versus 1/11 [9.1%]; $p = 0.003$), whereas this was not significant for PIP joints treated (7/25 [28%] versus 0/10; $p = 0.069$). The median time to reach the primary endpoint in the CCH arm was 57 days[19]. After the last injection in the double-blind or open-label phase, the primary endpoint was met in 68/134 (50.7%) of cords treated with CCH (67.7% of MP joints and 36.1% of PIP joints). No recurrence of contracture was seen in this study[2].

A company-performed post-hoc analysis of CORD I and CORD II found that 116/166 (67%) patients with ≤ 2 affected joints reached primary endpoint in the primary cord.

### 1.3 Additional studies

In support of the pivotal studies described above, the company submission also provides details of four additional phase III trials and three phase II trials[2]. Results from these trials are summarised in Appendix 1.

### 3.1.4 Systematic review and informal comparison

The submission included details of a systematic review conducted by the company to evaluate the published literature available on the efficacy and safety of treatment options for Dupuytren's contracture[2]. A total of 110 publications were identified that discussed one or more treatment (fasciectomy, n = 86; fasciotomy [needle or open] n = 14; CCH, n = 7; other surgery, n = 5). A systematic review by Becker et al. (2010) was also highlighted and discussed in the company submission[20].

The majority of surgical studies identified were single-arm observational studies; all comparative studies identified compared different surgical techniques. A total of six randomised controlled trials (seven publications[21–27]) of varying quality were identified, which evaluated the efficacy and safety of fasciectomy. These were compared with the phase three trials of CCH published by the company. Patient numbers for fasciectomy studies (maximum n = 113) were smaller than for CCH studies (maximum n = 308). There is considerable variation in endpoints, definitions and population denominators used between the studies; therefore comparison of results across studies is difficult and subject to considerable bias, as highlighted in a previous systematic review[20]. As a formal statistical comparison was not possible, an informal comparison of the data available has been provided by the company (Table 1)[2].

**Table 1. Informal comparison of outcomes from fasciectomy and CCH randomised controlled trials[2].**

| Study | Treatment type | Mean joint contracture improvement | | | Range of motion improvement | | | Recurrence | |
|---|---|---|---|---|---|---|---|---|---|
| | | Overall | PIP joint | MP joint | Overall | PIP joint | MP joint | FU | % |
| CORD I[5] | CCH | 79.3% | 64.5% | 87.1% | 36.7° | 29.0° | 40.6° | 2 years | 19.3%*[28] |
| CORD II[19] | CCH | 70.5% | NR | NR | 35.4° | 31.8° | 40.0° | | |
| Citron (2005)[25] | Fasciectomy (using Bruner skin incision) | 55.4%† | NR | NR | NR | NR | NR | 2 years | 32% |
| Citron (2005)[25] | Fasciectomy (using z-plasty skin incision) | 57.9%† | NR | NR | NR | NR | NR | 2 years | 18% |
| Degreef (2010)[23] | Segmental fasciectomy with tamoxifen | NR | NR | NR | 32% | NR | NR | NR | NR |
| Van Rijssen (2006)[21,22] | Limited fasciectomy | 79% | 49% | 87% | NR | NR | NR | 5 years | 23.8% |
| Ullah (2009)[26] | Fasciectomy | NR | NR | NR | NR | 30.4°†† | NR | 3 years | 10.9% |

CCH = collagenase *Clostridium histolyticum*; FU = follow-up; MP = metacarpophalangeal; NR = not reported; PIP = proximal interphalangeal

*** This result is taken from the CORDLESS study which also includes results from the JOINT I and JOINT II studies (see Appendix 1)[28]**

† Calculated using mean pre and post-operative deformities using the following formula: (preoperative - postoperative deformity)/preoperative deformity*100; defined as improvement in Total Passive Extension Deficit (TPED).

†† Calculated based on a range of movement of 34.6° pre-operatively and 65° at three years.

Note: Hazarika 1979 and Howard 2009 have been omitted since no comparable results were presented.

### 3.1.5 Comparative safety

In CORD I, 198/204 (97.1%) patients in the CCH arm reported adverse events (AEs) compared with 49/104 (47.1%) in the placebo group. Serious AEs (SAEs) were reported in seven patients who received CCH, with three deemed to be treatment-related: one case of complex regional pain and two tendon ruptures. Four patients discontinued treatment due to AEs. In CORD II, 45/45 (100%) patients in the CCH arm reported AEs compared with 12/21 (57.1%) in the placebo group[2]. During the double-blind phase, one treatment-related SAE was reported: a flexion pulley rupture of the left small finger which subsequently underwent PIP joint arthrodesis and tenotomy. During the open-label phase, ten SAEs were reported in the CCH arm, with two deemed treatment-related: one patient experienced sensory abnormality and required surgery for thickening and proliferation of the Dupuytren's cord[19]. No patients discontinued study drug due to AEs[2].

CCH-treated patients reported significantly more injection- and manipulation-related AEs, including contusion, injection-site haemorrhage, injection-site pain, peripheral oedema and ecchymosis, than placebo-treated patients (all comparisons $p \leq 0.02$). In general, most AEs were mild to moderate in intensity and resolved without intervention. There were no clinically meaningful systemic allergic reactions in either study[2,19].

Comparison of the systematic review data shows divergent safety profiles between CCH and fasciectomy, due to the distinct nature of treatment. In the studies identified, and as reported by Becker et al., fasciectomy was found to lead to intraoperative and postoperative complications such as nerve injury, wound infection and complex regional pain syndrome[20–27], and in general tended to be associated with a higher rate of major complications than CCH treatment[2].

### 3.2 WMP critique

- As demonstrated in the pivotal phase III trials CORD I and CORD II, CCH is effective in treating Dupuytren's contracture across a wide severity range, with a tendency for greater effect in less severe contracture: in CORD I and CORD II, a greater percentage of patients with less severe contracture (< 50 degrees) achieved the primary endpoint. Effectiveness was also more clearly demonstrated for MP than PIP joints, irrespective of disease severity[5,19].
- Surgical procedures, including fasciectomy, can be complex and may result in significant perioperative and/or post-operative complications. Fasciectomy is an invasive procedure with a prolonged recovery time (ranging from 21 to 58 days[29–32]). The majority of CCH-related AEs reported in CORD I and CORD II were non-serious, confined to the treated area and resolved in a short time period. CCH treatment can be performed in an outpatient setting and has an expected recovery time of 1–2 weeks[2].
- The company have restricted their submission to the use of CCH as an alternative to fasciectomy. However, no studies of CCH versus fasciectomy are presented in the company submission. An informal comparison of the clinical effectiveness and safety profiles of the treatments was provided; however, the outcomes assessed did not include the primary endpoint that was assessed for CCH[2]. The Committee for Medicinal Products for Human Use (CHMP) accept that the efficacy profile of CCH is similar to that seen with surgical procedures, and that the safety profile is better than fasciectomy and generally similar to PNF[33].
- CHMP state that the available efficacy and safety data suggest that CCH is intended for the same category of patient as PNF[33]. PNF was recommended by NICE in 2004 in the absence of a non-surgical option. The company state that CCH should not be considered in patients for whom PNF is considered

appropriate; therefore, no comparative clinical or cost data (see Section 4) for CCH versus PNF are included in the submission.

- Contracture of at least 20 degrees in either joint was an inclusion criterion of both CORD I and CORD II; whereas patients are generally considered for surgery with contracture at any degree in the PIP joint but > 30 degrees in the MP joint[2,4,8,34].
- Despite the incidence of Dupuytren's disease being highest in people of Northern European descent, JOINT II was the only study that enrolled European patients (n = 137) (see Appendix 1). However, the company submission states that a sub-group analysis demonstrated no difference in the efficacy and safety of CCH between US, Australian and European patients[2].
- Long-term data regarding rate of recurrence, safety, impact of repeat treatment, hand functionality, complications and immunogenic potential are lacking. No quality of life data are provided[33].
- No adjusted odds ratio or confidence intervals are reported. CHMP deemed this acceptable as results for secondary variables allow additional confirmation of the clinical relevance[33].

## 4.0 SUMMARY OF EVIDENCE ON COST-EFFECTIVENESS

### 4.1 Cost-effectiveness evidence

#### 4.1.1 Context

The company submission describes a cost-minimisation analysis of CCH compared to fasciectomy (open surgical procedure) for the treatment of adult patients with Dupuytren's contracture with a palpable cord[2]. PNF, which is a less invasive procedure than fasciectomy and can be performed in an outpatient setting[18], is not considered as a comparator. Therefore, the company has implicitly limited its submission to patients in whom PNF is not an option. The submission is further limited to a selected subgroup of patients with a maximum of two affected joints, using up to three injections per cord, with no more than six injections per patient.

In the absence of direct comparative data, or robust indirect comparative data, the analysis is based on the assumption of equivalent efficacy and safety for CCH and fasciectomy treatment. An informal, qualitative comparison has been made between the available fasciectomy outcome data identified via a systematic literature review and data from a subgroup of patients enrolled in the CORD I and II placebo-controlled trials who received CCH treatment for a maximum of two affected joints using up to a maximum of three injections per cord. The base case analysis assumes that patients will receive on average 1.92 doses of CCH and no physiotherapy will be required. The cost of fasciectomy includes physiotherapy sessions, and the analysis assumes that patients will be treated with only one surgical procedure over the one-year time horizon that is considered. See Appendix 2 for further details.

### 4.1.2. Results.

Results of the base case analysis are shown in Table 2.

**Table 2. Company-reported results of cost-minimisation analysis of CCH versus fasciectomy for the treatment of adult patients with Dupuytren's contracture**

| Base case costs | CCH | Fasciectomy |
|---|---|---|
| Drugs | 1.92 × £650 | N/A |
| Administration/surgery | 1.92 × £143 | £2,568 |
| Appointments | 1.92 × £86 | £86 |
| Physiotherapy | N/A | £320 |
| **Total cost*** | **£1,688** | **£2,974** |
| **Average saving per patient treated with CCH instead of fasciectomy** | **£1,286** | |

N/A = not applicable
* Based on 1.92 CCH injections assumed per patient; or one surgical procedure per patient per year

A range of one-way sensitivity analyses were conducted to address variation in the number of injections, use of in-patient palmar fasciectomy for all patients, different proportions of CCH patients undergoing day case treatment, treatment of patients presenting with ≤ 3 affected joints, and the use of NHS reference costs as an alternative to the Payment by Results (PbR) tariff.

Varying the mean number of injections showed that CCH remains cost saving when the mean number of injections is less than 3.4. If all patients were to be treated with palmar fasciectomy as an in-patient procedure (lower tariff), rather than in the out-patient setting, CCH would still save on average £815 per patient when using an average of 1.92 injections. If 95% of patients receive CCH injections as a day-case treatment, this would still be cost-saving (£47 per patient) compared to fasciectomy. When the proportion of patients with three affected joints was included in CCH treatment, the average number of injections per patient increased to 2.26 but still remained cost-saving compared to fasciectomy. Cost savings using the NHS reference costs were lower than those estimated using PbR tariff prices. Few multi-way sensitivity analyses are presented to explore combined uncertainty in several parameter values.

### 4.1.3 WMP critique

Strengths of the economic evidence include:

- The company submission is transparent regarding the calculations for the cost-minimisation analysis.
- A systematic literature review was conducted to identify relevant outcomes data for the surgical comparator.

Limitations of the economic evidence include:

- There is a lack of data with which to reliably compare the relative efficacy and safety of CCH and fasciectomy. The company has conducted a cost-minimisation analysis on the assumption of equivalence of clinical efficacy and safety. A cost utility analysis (CUA) approach would permit greater exploration of uncertainty in those outcomes that are simply assumed to be equivalent within the CMA framework, and may better capture the substantial differences in treatment approaches, although data with which to inform a CUA

would also be very limited. No sensitivity analyses were conducted around the assumption of equivalence.

- PNF (NICE guidance IPG43[18]) is a less invasive and possibly less costly procedure than fasciectomy, and CHMP considered that the available efficacy and safety data suggest that CCH treatment is intended for the same category of patient as PNF[33]; however, the company has not considered PNF as a comparator. The economic evidence submitted by the company would have been more complete had a comparison against PNF being made. In its absence, the evidence appears to relate only to those cases where PNF is not considered a viable treatment alternative.
- The modelled treatment pathway is limited, and the company submission does not consider treatment options upon failure following fasciectomy or repeated CCH treatment.

### 4.2 Review of published evidence on cost-effectiveness

Standard literature searches have not identified any published economic evidence on the cost-effectiveness of CCH compared to fasciectomy for the treatment of adult patients with Dupuytren's contracture with a palpable cord.

## 5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

### 5.1 Budget impact evidence

#### 5.1.1 Context and methods

The budget impact analysis relates to the use of CCH in a selected subgroup of patients with a maximum of two affected joints, as in the cost minimisation analysis above. Due to lack of data on the prevalence of Dupuytren's contracture in Wales, the company assumes a mean prevalence of 10.7%, based on literature reports from six countries[35]. This would suggest around 321,000 people could be affected by Dupuytren's contracture in Wales. Based on an incidence rate of 32.5 per 100,000 population per year, derived from a single UK health board audit (Derby Hand Audit)[15], the company estimates there would be 975 newly diagnosed patients each year in Wales. A simple assumption is made that only incident cases would be eligible for treatment, and of these 63% would be referred for surgery (reportedly based on the UK audit of surgery). It is further assumed that, based on the CORD I and II trials, 46% of those patients referred for surgery would have less than three affected joints. This equates to 283 patients with two or less affected joints that would be eligible for CCH treatment. Assuming that the uptake of patients will increase from 20% in year one to 100% in year five, the estimated number of patients treated by CCH would increase from 57 to 283 over the five-year period. Using the cost savings estimated in the base-case cost minimisation analysis above, this would result in cost saving of £73,302 in year one, increasing to £363,938 in year five (see Table 3).

**Table 3. Company-reported costs associated with CCH treatment**

| | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 |
|---|---|---|---|---|---|
| Number of eligible patients | 283 | 283 | 283 | 283 | 283 |
| Uptake % | 20% | 40% | 60% | 80% | 100% |
| Number of treated patients | 57 | 113 | 170 | 226 | 283 |
| **Overall net costs** | **-£73,302** | **-£145,318** | **-£218,620** | **-£290,636** | **-£363,938** |

No scenario analysis addressing the uncertainty associated with budget impact estimates is provided in the company submission.

### 5.1.2 WMP critique of the company's budget impact estimates

Due to lack of Welsh-specific data on the prevalence and incidence of Dupuytren's disease, the number of patients eligible for CCH treatment is subject to considerable uncertainty. According to the company's conservative estimates, only *de novo* patients would be treated with CCH. However, since CCH treatment is less invasive than fasciectomy, a number of existing patients with Dupuytren's contracture may prefer CCH treatment to surgery. Since CCH is indicated for patients with palpable cord only, 100% uptake rate for CCH treatment seems unrealistic. As the cost elements of the budget impact analysis are derived from the cost minimisation analysis, the limitations and uncertainties outlined in Section 4 and Appendix 2 would impact upon the cost savings reported. Due to the wide range of assumptions employed, the reliability of the company's estimated budget impact is unclear.

## 5.2 Comparative unit costs

Currently there are no other pharmacological treatments licensed for Dupuytren's contracture.

**Table 4. Example of drug acquisition costs for the treatment of adult patients with Dupuytren's contracture with a palpable cord**

| Regimen | Example of a single dose* | Cost per injection |
|---|---|---|
| Xiapex® (Collagenase Clostridium histolyticum) 0.9 mg powder and solvent for injections | 0.58 mg per injection | £650 |
| **Only one cord must be treated at a time. See the Summary of Product Characteristics for full dosing details[1].*<br>*Cost based on MIMS list price[36].* | | |

# 6.0 ADDITIONAL INFORMATION

## 6.1 Shared care arrangements

WMP is of the opinion that CCH is not suitable for shared care within NHS Wales.

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## Appendix 1. Additional clinical information

### Table 1. Summary of studies included in company submission[2]

| Study | Study type | Study size | Inclusion criteria | Treatment regimen | Endpoint(s) | Outcome(s) |
|---|---|---|---|---|---|---|
| **Phase III** | | | | | | |
| DUPY-303/404[37–39] | Double-blind, randomised, placebo-controlled study followed by an open-label extension | n = 35 (28 male, 7 female), single US centre<br><br>Open-label phase: n = 19 | Fixed-flexion contracture of at least 20° | Patients could receive up to three injections of 0.58 mg CCH or placebo (2:1) in double-blind phase. Patients could receive up to three injections in a single cord and a maximum of five injections in the open-label phase. | Reduction in joint contracture to ≤ 5° 30 days after injection | CCH: 16/23 patients met endpoint after one injection. 21/23 met endpoint after three injections.<br>Placebo: No patients met endpoint after three injections. ($p < 0.001$)<br><br>MP joint: 12/14 met endpoint after three CCH injections.<br>PIP joint: 9/9 met endpoint after three injections.<br><br>Open-label phase: 27/35 joints (14/16 MP and 13/19 PIP) met endpoint. At 12 months, recurrence was seen in 1 MP and 4 PIP joints.<br><br>The AE profile was similar to that seen in pivotal studies[2]. No treatment-related deaths or discontinuations were recorded. |
| JOINT I (AUX-CC-856)[40] | Open-label, single-arm | n = 201 (164 male, 37 female), 14 US centres | Fixed-flexion contracture of ≥ 20° or ≤ 100° for MP and ≥ 20° or ≤ 80° for PIP | Patients could receive up to five 0.58 mg CCH injections with a maximum of three in a single cord | Reduction in joint contracture to ≤ 5° 30 days after injection | 154/292 joints met endpoint (126/188 MP and 28/104 PIP, receiving an average of 1.2 and 1.4 injections, respectively). Recurrence was seen in 11/154 joints which met the endpoint.<br><br>The AE profile was similar to that seen in pivotal studies[2]. No treatment-related deaths or discontinuations were recorded. |
| JOINT II (AUX-CC-854)[41] | Open-label, single arm | n = 386 (334 male, 52 female), 20 centres in Australia, UK, Switzerland, Sweden, Denmark and Finland | Fixed-flexion contracture of ≥ 20° or ≤ 100° for MP and ≥ 20° or ≤ 80° for PIP | Patients could receive up to five 0.58 mg CCH injections with a maximum of three in a single cord | Reduction in joint contracture to ≤ 5° 30 days after injection | 343/587 joints met endpoint (243/343 MP and 100/244 PIP, receiving an average of 1.2 and 1.3 injections, respectively). Recurrence was seen in 8/343 joints which met the endpoint.<br><br>In the European sub-group, 109/214 (50.9%) joints met endpoint (73/119 MP and 36/95 PIP, receiving an average of 1.3 injections for both). Recurrence was seen in 2/109 joints which met the endpoint.<br><br>The AE profile was similar to that seen in pivotal studies[2]. No treatment-related deaths or discontinuations were recorded. |

**Table 1 continued.**

| Study | Study type | Study size | Inclusion criteria | Treatment regimen | Endpoint(s) | Outcome(s) |
|---|---|---|---|---|---|---|
| CORDLESS (AUX-CC-860): two-year follow-up[28] | Ongoing non-treatment study in which subjects previously treated with CCH in CORD I, CORD II, JOINT I and JOINT II are monitored yearly for safety and recurrence | n = 634, multiple centres in US, Australia, UK, Switzerland, Sweden, Denmark and Finland | Received at least one injection of 0.58 mg CCH and at least one fixed-flexion contraction measurement after treatment. | N/A | Recurrence, defined as an increase in contracture of ≥ 20° or further medical or surgical intervention. | 119/619 joints (61/449 MP and 58/170 PIP) had recurrence. 13/619 required surgical correction.<br><br>AEs and SAEs were experienced by 3.6% and 1.3% of subjects, respectively. None were deemed related to treatment. No treatment-related deaths or discontinuations were recorded. |
| **Phase II** | | | | | | |
| DUPY-101[42] | Double-blind, randomised, placebo-controlled | n = 49 (42 male, 7 female), single US centre | Adults with Dupuytren's contracture | Single dose 0.58 mg CCH or placebo (1:1) | Reduction in joint contracture to ≤ 5° 30 days after injection | MP joint: Endpoint met in 78% CCH versus 11% placebo<br>PIP joint: Endpoint met in 71% CCH versus 0% placebo |
| Badalamente & Hurst 2000[43] | Pilot dose escalation study followed by open-label, single-arm phase | n = 35 (32 male, 3 female) | Adults with Dupuytren's contracture | Dose escalation (n = 6): One dose CHH at 300 U, 600 U, 1,200 U, 2,400 U, 4,800 U or 9,600 U was given to each patient (1:1:1:1:1:1)<br><br>Open-label phase: 10,000 U (0.58 mg) (n = 29) | Joint correction to normal (0°) within 1 to 14 days of injection | Dose escalation: No clinical effect was seen at doses <10,000 U (0.58 mg)<br><br>Open-label phase:<br>Efficacy:<br>MP joint: 28/34 met endpoint<br>PIP joint: 4/9 met endpoint<br><br>Safety: No SAEs reported. AEs reported included tenderness to pressure at injection site with palmar, and sometimes dorsal, oedema and haematoma. All symptoms resolved within 1–2 weeks of injection. |

| Study | Study type | Study size | Inclusion criteria | Treatment regimen | Endpoint(s) | Outcome(s) |
|---|---|---|---|---|---|---|
| DUPY-202[44] (with eight-year follow-up study[45]) | Randomised, placebo-controlled dose response study with eight-year follow-up study | n =80 (64 male, 16 female)<br><br>Follow-up study n = 8 | Fixed-flexion contracture of ≥ 20° to ≤ 30° | Single dose CCH (2,500 U, 5,000 U or 10,000 U) or placebo (1:1:1:1) | Reduction in joint contracture to ≤ 5° 30 days after injection | Endpoint met in:<br>50% of cords that received 2,500 U<br>45% of cords that received 5,000 U<br>78% of cords that received 10,000 U<br><br>AEs were of mild or moderate severity, non-serious, transient and resolved within a short period without sequelae.<br><br>5/8 patients in follow-up study had received a 10,000 U (0.58 mg) dose of CCH<br>2/4 MP joints experienced recurrence<br>1/1 PIP joints experienced recurrence |
| AE = adverse event; CCH = collagenase *Clostridium histolyticum*; MP = metacarpophalangeal; PIP = proximal interphalangeal; SAE = serious adverse events.<br>Note: The licensed dose of CCH is referred to as 0.58 mg, which is equivalent to 10,000 U | | | | | | |

## Appendix 2. Additional health economic analysis information

### Table 1. Health economic analysis detail[2]

| | Base case model | Appropriate? |
|---|---|---|
| **Comparator(s)** | Fasciectomy (including palmar and digital fasciectomy) as a surgical comparator. | The company based their choice of comparator on the high prevalence of fasciectomy in the treatment of DC in England[3] and expert opinion[2]. PNF, which is a less invasive[18] (and possibly less costly) procedure than fasciectomy, is not considered as a comparator. Therefore, the submission is limited to the use of CCH in patients in whom needle fasciotomy is not considered to be an option.<br><br>CHMP considered that the efficacy of CCH had been demonstrated in patients with a wide range of severities. However, CHMP also states the available efficacy and safety data suggest that CCH is intended for the same category of patient as PNF[33]. |
| **Population** | Adult patients with Dupuytren's contracture with a palpable cord. | Yes, in line with the licensed indication[1]. However, the comparator chosen by the company limits the submission to the use of CCH in patients in whom needle fasciotomy is not an option. The submission is further limited to a selected subgroup of patients with a maximum of two affected joints, using up to three injections per cord, with no more than six injections per patient. |
| **Analysis type** | CMA of CCH treatment versus fasciectomy (using weighted average cost of palmar and digital fasciectomy). | CMA is appropriate only when all domains of health outcomes may reasonably be considered to be equivalent. There is a lack of head-to head comparative data for CCH treatment and fasciectomy, since pivotal studies CORD I and CORD II were placebo-controlled[2]. There are limited data on long-term effects of CCH treatment and the recurrence rate in CCH-treated patients. Little consideration is given to potential differences in adverse effects, recovery time and patient preferences for treatment approaches (CCH treatment is less invasive than open surgery) when assuming equivalence. Therefore, there is little evidence to support the assumption of equivalence between the two treatment approaches or the CMA approach. |
| **Perspective** | Considers direct medical costs only, from the perspective of NHS Wales. | Yes. |
| **Time horizon** | The company assumes a time horizon of one year for the CMA. | Dupuytren's contracture often recurs, and data are available for two-year recurrence rates. A longer time horizon would have been appropriate. |
| **Discount rate** | Was not applied. | Discounting is not relevant for the assumed time horizon of one year (although the time horizon may not be sufficient to capture all relevant costs and outcomes). |

## Table 1 continued

| | Base case model | Appropriate? |
|---|---|---|
| **Efficacy** | The CMA approach implicitly assumes equivalence between fasciectomy and CCH in terms of efficacy (and other domains of health outcomes). An informal, qualitative comparison of efficacy data relating to fasciectomy (identified via a systematic literature review) is used to support the assumption of equivalence. | There is a lack of data available to robustly determine the relative efficacy of CCH and fasciectomy. There are no direct comparative trials of CCH treatment against surgery (or any other treatment approaches). The assumption of equivalence between CCH and fasciectomy is based on an informal qualitative comparison of efficacy data identified via a systematic literature review, using selected outcome measures (e.g. the reduction in contracture from baseline – a secondary endpoint in the pivotal trials of CCH), which the company acknowledges has limited validity[2]. Formal comparative methods are not considered feasible due to the limited data available in support of fasciectomy, which are mainly non-comparative studies. The CHMP considered that CCH had demonstrated a treatment success rate similar to the current mainstay of treatment and that CCH provides an alternative option to surgery. However, CHMP also states the available efficacy (and safety) data suggest that CCH is intended for the same category of patient as PNF[33]. |
| **Adverse effects** | Adverse events were not included in the CMA, since CCH treatment and fasciectomy were considered by the company to be clinically equivalent. | There is a lack of comparative adverse event data available, and the implicit assumption of the CMA framework is that adverse events are equivalent between the treatment approaches. However, the company submission notes that the types of adverse events common to fasciectomy (open surgery) are not necessarily observed with the less invasive CCH treatment[2]. Therefore, the assumption of equivalence in adverse event profiles would seem debatable. |
| **Utility values** | Utility values were not used, since a CMA was presented. | Yes, but only if the CMA approach was considered to be appropriate (but see above). |
| **Resource use and costs** | Estimates of the number of CCH injections are based on a subset of patients in the CORD I and CORD II studies, i.e. those who received treatment for a maximum of two joints, using a maximum of three injections per cord. Costs of CCH treatment include the cost of drug and administration and one follow-up visit; physiotherapy is assumed not to be required. Fasciectomy costs include cost of surgery (based on weighted average of digital and palmer fasciectomy procedures, and inpatient and outpatient settings using hospital episode statistics – assumed to be one surgical procedure per year), one follow-up visit and physiotherapy costs, reportedly based on an audit of treatment in the UK. Published unit costs data are used. | Appropriate items of resource use appear to have been considered if the CMA framework is considered appropriate (but see above). The modelled cost of CCH treatment includes only one follow-up visit post treatment. However, a follow up visit would be required the day after injection and at 30 days (to determine whether further treatment with CCH is required).<br><br>The company considers the assumption of only one surgical procedure per year to be conservative as a review of UK practice is reported to indicate a quarter of patients underwent more than one procedure within 12 months. |

## Table 1 continued

| | Base case model | Appropriate? |
|---|---|---|
| **Uncertainty and scenario analyses** | Sensitivity analyses were conducted varying the mean number of injections, use of inpatient palmar fasciectomy for all patients, different proportions of CCH patients undergoing day case treatment, treatment of patients with ≤ 3 affected joints, addition of an injection to patients crossed over from placebo, and the use of NHS reference costs as an alternative to PbR tariff. | A range of one-way sensitivity analyses are presented, but only in relation to costs. These indicate that CCH remains cost saving: while the mean number of injections remains below 3.3 per patient; under the assumption that all patients undergoing fasciectomy are treated using the least costly surgical procedure (within the PbR tariff); under the assumption that 95% of patients who receive CCH do so as day cases rather than as outpatients; and when costs are based on NHS reference costs rather than PbR tariff costs.<br><br>Few multi-way analyses have been conducted to explore combined uncertainty across multiple parameters. |
| **Model provided?** | Yes. | Yes. |
| CCH = collagenase *Clostridium histolyticum*; CHMP = Committee for Medicinal Products for Human Use; CMA = cost minimisation analysis; DC = Dupuytren's contracture; PbR = Payment by Results; PNF = percutaneous needle fasciotomy. | | |