



**North East Treatment
Advisory Group**

**Collagenase (Xiapex®)
for Dupuytren's Contracture**

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Summary

Collagenase (Xiapex®, Pfizer) is an enzyme which is injected directly into collagenous cords causing finger-joint contraction in more severe cases of Dupuytren's disease, known as Dupuytren's contracture. It is the first pharmacological treatment licensed for Dupuytren's contracture.

Existing treatment options for more severe cases of Dupuytren's contracture consist of several surgical interventions ranging from the relatively conservative fasciotomy to more radical fasciectomy and dermofasciectomy. In severe cases a digit may be amputated. The recurrence rate after surgery is high. Post-surgical care consists of splints for up to three months and manual physiotherapy.

Collagenase has demonstrated efficacy in several high-quality placebo-controlled studies. These studies demonstrated high rates of efficacy although repeated treatments are often required to achieve the stringent measure of clinical success and follow-up is relative short. Longer term follow-up data, whilst limited, indicates a recurrence rate comparable to, and not exceeding, that which would be expected with existing surgical treatments.

Collagenase injections and subsequent digital extension are associated with a high burden of adverse effects although most are localised, mild or moderate in severity and transient. In rare cases more serious effects such as tendon rupture (estimated 0.1% incidence) have occurred.

Collagenase has not been directly compared with any surgical treatment.

Collagenase is a costly treatment at £780 per injection. Outpatient appointments are required for administration and subsequent digital extension. Only one injection can be administered at a time. However, the predominant surgical intervention, palmar fasciectomy, is estimated to cost between £2,500 and £5,000 per case with additional costs for splints and physiotherapy. It is estimated that most cases can be treated with, on average, two injections of collagenase at a combined cost of less than £2,000. Therefore collagenase treatment of Dupuytren's contracture could prove to be less costly than surgical interventions for many cases.

Targeted treatment strategies could be employed to increase the likely cost-effectiveness of collagenase compared with surgical treatment. These may include less severe contractions, specific joint types, patients with fewer affected joints, and excluding patients who might otherwise receive less invasive surgical treatment.

Introduction

Dupuytren's disease is a condition affecting the hands and fingers resulting in symptoms such as lumps and dimples and other changes to, or thickening of, skin on the palm, and tenderness. Dupuytren's contracture is a complication of the disease. Initially, nodules develop in the connective tissue under the skin on the palm of the hand. Over time, which may be months or several years, these nodules can grow into cords of contracted fibrotic tissue containing primarily collagen. This can make it difficult for patients to fully extend their fingers. Affected fingers will eventually become permanently fixed in a bent (contracted) position. Severe Dupuytren's contracture is therefore a disfiguring and sometimes painful deformity resulting in permanently contracted (bent) fingers which cannot be straightened without invasive medical intervention.^{1,2}

The most commonly affected joints are the proximal interphalangeal (PIP) joints (these are the joints immediately above the knuckles) and the metacarpophalangeal (MP) joints (these are the knuckle joints). Although any finger can be involved the most commonly affected, in order, are the ring finger, little finger and middle finger. More than one joint may be affected on a single hand, and more than one hand may be affected at any one time. A strong genetic preponderance has been identified and the condition is most common in white Europeans. A typical patient would be a white male in the 6th or 7th decade of life.

Most patients will not require treatment because their condition is mild. However more severe contractures can affect normal hand function and in these cases the predominant treatment option is currently surgical fasciectomy. More conservative surgery consists of needle fasciotomy which can be carried out as an outpatient procedure and involves one or more cords being divided with a blade or needle. The more radical fasciectomy, potentially a day case procedure but often performed on an inpatient basis, will include removal of the thickened connective tissue. It is used in more severe cases. Following hand surgery patients will require the digit to be splinted and hand physiotherapy is commenced. Night splints are often required for up to three months. Recurrence rates are high with surgery, reported as up to 60%. In extreme cases digit amputation is applied.¹⁻³

Radiation therapy is sometimes used in less advanced Dupuytren's disease with the aim of preventing or reducing contracture. It is believed to affect the cells which produce collagen.⁴

Xiapex® is the first pharmacological treatment licensed for the treatment of Dupuytren's contracture. It contains collagenase isolated from *Clostridium histolyticum* bacteria. It is specifically licensed for the treatment of Dupuytren's

contracture in adult patients with a palpable cord. It is administered as a small volume injection directly into the cord. Approximately 24 hours after administration of Xiapex® patients should undergo digit extension under medical supervision with the aim of regaining full flexion of the digit. A repeat injection and manipulation may be performed in the same cord after an interval of at least four weeks if deemed clinically necessary. Injections and extension procedures can be administered up to a maximum of three times per cord. Xiapex® is licensed for treatment of only one cord at a time. If multiple cords require treatment these must be treated sequentially.⁵

Collagenase for Dupuytren's contracture is not currently planned for appraisal by NICE and a clinical desire to use the treatment within more than one NHS North East centre has been identified. Therefore NETAG has been requested to conduct an appraisal of, and issue a recommendation for, the use of collagenase (Xiapex®) within its licensed indication for Dupuytren's contracture.

Clinical evidence

The primary sources of evidence for the efficacy of collagenase in Dupuytren's contracture are two parallel studies known as CORD-1 and CORD-2 (collagenase option for reduction of Dupuytren's).^{6,7}

Both studies were double-blind randomised placebo-controlled studies in patients with predominantly moderate to severe Dupuytren's joint contractures of between 20° and 80° from the horizontal digital plane.

In CORD-1 203 patients were treated with collagenase and 103 with placebo. The patients group was predominantly male (80%), white (99%), and had a mean age of 63 years. About one-third of patients had at least one contracture in both hands with a mean of three affected joints. About 40% of patients had previously been treated with surgery for Dupuytren's contracture although not necessarily in the same cord being injected within the study. The primary end point was the proportion of all primary joints with a contraction angle of $\leq 5^\circ$ thirty days after last injection. This demonstrated efficacy of 64% with collagenase vs. 7% with placebo ($p < 0.001$). The mean change in range of motion from baseline was 37° with collagenase vs. 4° with placebo ($p < 0.001$). Efficacy was greater for MP joints compared with PIP joints. A mean of 2.17 collagenase injections were administered per patient including in non-primary joints. 39% of patients met the primary efficacy end point after the first collagenase injection.⁶

CORD-2 was similar in design to CORD-1 but smaller in scale; 45 patients received collagenase and 21 received placebo injections. The patient group was predominantly male (85%), exclusively white, and had a mean age of 64 years. About half of patients had at least one joint contracture in each hand, with a mean of 3.3 affected joints per patient. CORD-2 had a higher proportion of patients with PIP joint contractures than CORD-1. Over half of patients had previously received surgery for Dupuytren's contracture although not necessarily in the same cord being injected within the study. The primary endpoint was the same as in CORD-1, and demonstrated efficacy of 44% with collagenase vs. 5% with placebo ($p < 0.001$). The mean change in range of motion from baseline was 35° with collagenase vs. 8° with placebo ($p < 0.001$). Efficacy was significantly greater in MP joints compared with PIP joints. After 12 months, 134 cords of 134 joints had been injected with collagenase. The proportion with contraction $\leq 5^\circ$ thirty days after the last injection was 51%; efficacy was higher for MP joints compared with PIP joints (68% vs. 36%). After 12 months no joint had demonstrated recurrence of contracture defined as contraction $\geq 20^\circ$ from the horizontal plane and a palpable cord.⁷

Earlier evidence is available from a small double-blind placebo-controlled randomised study with an open-label extension phase. 23 patients received treatment with collagenase and 12 with placebo (mean joint contraction of 50°). The primary endpoint was the same as used in the CORD studies and, in the double-blind phase with a mean of 1.4 injections (range 1 to 3), demonstrated efficacy of 91% vs. 0% ($p < 0.001$). In the extension phase, which included 19 patients and 35 joints, 17 patients (90%) achieved clinical success in at least one joint.⁸

Longer term (12 month) recurrence from the 'entire phase 3 clinical programme' is reported as having been assessed in 830 successfully treated joints (i.e. contraction $\leq 5^\circ$). After adjusting for the various follow-up periods, the projected mean rate of recurrence of contraction $\geq 20^\circ$ was 6.7%.⁹

Extensive follow-up of eight years is provided in a report of eight patients who had been treated within clinical studies. Six patients had received treatment for a MP joint and two for a PIP joint contraction. In MP patients, the mean baseline contraction was 57° which had initially reduced to 9° but increased to 22° by eight years (range 0° to 55°). Four MP patients had a recurrence defined as contraction $\geq 20^\circ$. In the two PIP joint patients, mean baseline contraction was 45°, initially reduced to 8° but increased to 60° at eight years, with both experiencing recurrence. In both groups of patients the mean contraction demonstrated steady increases from the initial reduction one-week after injection, through six months, 12 months and then at eight years.¹⁰

A systematic review comparing open fasciectomy, needle fasciectomy and collagenase injections for Dupuytren's contracture found that all treatments are associated with a high rate of recurrence and complications. The recurrence rate was higher for needle fasciectomy (50 to 58% with mean follow-up of three to five years) compared with open fasciectomy (12 to 39%, mean follow-up 1.5 to 7.3 years; $p = 0.001$) which was itself significantly higher than that seen with collagenase injections (10 to 31%, mean follow-up four months to four years; $p = 0.001$). The complication rate ranged from 14 to 67% with open fasciectomy. Complications were not as extensively reported with needle fasciectomy and collagenase injections. Complications with these treatments consisted primarily of skin tears ranging from 9 to 25%. It is not possible to make conclusions about the superiority of one treatment over any other from this review due to study heterogeneity, especially with respect to follow-up. ¹¹

Safety

Adverse effects have occurred consistently across clinical studies. In the CORD studies the most common effects were swelling of the injected hand (peripheral oedema), bruising (contusion), pain in the injected hand, pain specifically at the injection site, bleeding at the injection site, swelling specifically at the injection site, tenderness, localised itching, and swollen lymph glands. The overall incidence of adverse effects was substantially greater in collagenase treated patients compared with placebo (any treatment-related event; ~100% vs. < 20 to 40%). Most adverse effects were mild or moderate in severity and related to relatively minor, transient and localised injection site reactions or digit-extension related events. ^{6,7} In CORD-1 (safety $n = 308$), 20 collagenase patients experienced a severe adverse event related to study drug compared with two placebo patients. Two tendon ruptures occurred in CORD-1, both requiring subsequent surgical intervention. ⁶ The tendon rupture rate is reported separately as 0.1%, with an incidence of three ruptures (including the two CORD-1 ruptures) across ~2600 injections in ~1000 patients. ⁹

Antibodies to either or both of the collagenase subtypes contained within Xiapex® occur with high frequency, reported as $\geq 85\%$ after one injection and 100% after two or more injections. ^{6,7} However no obvious clinical sequelae are associated with the emergence of these antibodies. ⁵⁻⁷ No severe allergic reactions have been observed in clinical studies of collagenase. ⁵

Systemic exposure resulting from collagenase injected into manual Dupuytren's cords is minimal. ⁵

Cost analysis

All costs include VAT at 20% where applicable unless otherwise indicated.

Xiapex® is available as a single use vial containing powder for reconstitution. Each vial costs £780.¹² The mean number of injections per affected joint, which is assumed to result in injection into the same cord, is reported as being about two.^{6,7,13}

Xiapex® is likely to be considered as an alternative treatment option to surgical intervention for moderate to severe Dupuytren's contracture. Over the five-year period April 2003 to March 2008 there were about 13,000 admissions per annum assumed to be for surgical treatment of Dupuytren's contracture in England.¹⁴ This equates to an estimated 650 per annum for NHS North East.¹⁵ It is unlikely that all these admissions would be treated with collagenase instead of surgical intervention. For example, some of these surgical interventions include digital amputations for which collagenase would not be a suitable alternative.

Adjusting this figure to exclude revisions and amputations provides an estimate of 624 admissions per annum for surgical interventions of Dupuytren's contracture within NHS North East.^{14,15}

The administration of collagenase and the subsequent extension procedure can feasibly be performed in an outpatient setting. Some assumptions of care will be made in calculating the cost of treatment with collagenase:

- Collagenase will be administered with a multi-professional outpatient follow-up appointment with digital extension performed with a single-professional outpatient follow-up appointment.
- A prior initial (first attendance) outpatient appointment has already been carried out for treatment assessment and will not be included.
- Relevant outpatient appointments will be costed using a 'trauma and orthopaedics' tariff code at £86 each, therefore two appointments cost £172. Note that this cost will vary if carried out under different specialities, e.g. with a 'plastic surgery' code the cost is £180, or £214 under a 'rheumatology' code.¹⁶ The available evidence indicates that most Dupuytren's surgical work in England is carried out using standard surgical tariff codes.¹⁴

The cost of two injections of Xiapex® plus the cost of four outpatient appointments is therefore assumed to be £1944 per case. Note that an individual patient may present as more than one case in any given period of time.

The cost of a day-case admission for palmar fasciectomy, the most commonly performed surgical procedure in England for Dupuytren's contracture, 'HB53Z:

Intermediate hand procedures for non-trauma category 2', is £2422. A small proportion of surgical interventions will require a revision, estimated at 7%, therefore the mean cost per patient including revisions is estimated at £2592.^{14,16}

Therefore the crude overall cost of treatment per case with Xiapex® is expected to be £648 less than surgery.

Note that the cost of surgery has been estimated conservatively, for example the cost of subsequent manual physiotherapy sessions is not included. No data regarding the nature or number of such appointments was identified and therefore it has not been possible to reliably estimate their cost. Further, data from one NHS North East commissioning cluster indicates that about half of all palmar fasciectomy are performed on an in-patient basis, and more than half are coded under 'HB51Z: Major hand procedures for non-trauma category 2' at £3,408 for a day-case admission or £5,108 for an elective inpatient admission ≤ 5 days.¹⁷ Both these factors would substantially increase the mean cost of surgery per case.

Other costs not included including the provision of splints which may be required with either collagenase or surgical interventions and the cost of any follow-up appointments with collagenase beyond the day immediately following injection.

Therefore the estimated difference between the treatment cost of Xiapex® vs. surgery of £648 per case should be interpreted as a likely minimum.

Surgery could be less costly than Xiapex® in some patients as only one cord can be treated at a time with Xiapex® whereas it is possible that multiple cords in the same hand could be treated in one surgical episode. Some of this variation is likely to be included within the assumption that a mean of two Xiapex® injections are administered per case.

Using the conservatively estimated cost of surgery for Dupuytren's contracture the cost of three or more Xiapex® injections (≥ £2,916) would be more costly than surgery. Pooled data from the CORD-1 and -2 studies indicates that about 20% of patients with only one or two affected joints (about 45% of the entire cohort) received ≥ 3 Xiapex® injections.

The cost of treating varying proportions of the NHS North East patient population (cases per annum) with collagenase compared with lower-cost surgery is demonstrated in table 1.

Table 1. Cost of collagenase (Xiapex®) treatment for estimated NHS North East patient populations (cases per annum).

Proportion of admissions treated with Xiapex® (n = 624)	Patients (n)	Collagenase (Xiapex®)			
		Two injections	Four orthopaedic follow-up outpatient appointments	Total cost	Saving compared with single surgical day-case admission (HB53Z)
10%	63	£98,280	£24,192	£122,472	£30,114
25%	156	£243,360	£59,904	£303,264	£74,568
33⅓%	208	£324,480	£79,872	£404,352	£99,424
50%	312	£486,720	£119,808	£606,528	£149,136

The efficacy, and thus cost-effectiveness, of Xiapex® can be enhanced by directing the treatment at patients who are expected to derive the most benefit: Evidence from the CORD studies consistently demonstrated that patients with less severe baseline contraction exhibited greater efficacy compared with those with the most severe contractions. In addition, MP joints demonstrated greater efficacy following treatment with collagenase compared with PIP joints.

Further, the net cost impact of Xiapex® can be optimised by directing treatment at patients who will be expected to require fewer injections, for example patients with only one or two affected joints. Indeed, the manufacturer of Xiapex® has recommended that it is targeted for use in patients with only one or two affected joints as part of a strategy to maximise the cost-effectiveness of the treatment. This strategy is based on post-hoc analyses of the CORD studies and appears to be both clinically and economically sound. Xiapex® could also be reserved only for patients who are expected to otherwise require the more invasive surgical procedures (fasciectomy) and not for the less invasive and less costly fasciotomies. However this will have a small net effect as fasciotomies account for only a small proportion (< 5%) of all surgical interventions for Dupuytren's contracture.¹⁴

There is no reliable evidence to demonstrate differences in efficacy between surgical treatments and collagenase injections therefore a cost-effectiveness analysis has not been performed.

Points to consider

Xiapex® is a first-in-class bacterium-derived injectable collagenase which has demonstrated high rates of efficacy in the treatment of Dupuytren's contracture in high quality placebo-controlled studies. However, there is a paucity of evidence with longer-term follow-up. The available evidence indicates relatively high rates of contraction recurrence, as is seen with established surgical interventions.

Xiapex® is associated with a large burden of adverse effects. These are generally associated with the injection and subsequent extension and tend to be mild or moderate in severity, localised, and transient. More severe but rarer effects have occurred such as tendon rupture. It is not clear whether the serious complication rate is greater with collagenase compared with surgical procedures. The available evidence indicates that the serious complication rate with collagenase is very low.

Xiapex® is a costly treatment at £780 per injection. Evidence from clinical studies indicates that patients require an average of two injections per case. In addition, Xiapex® will incur outpatient admission costs for administration and subsequent digital extension. The cost of Xiapex® is therefore estimated at nearly £2,000 per case. However, Xiapex® is likely to be considered only for those patients who might otherwise be treated with surgical interventions. The cost of surgery is estimated conservatively at about £2,500 per case meaning that Xiapex® is expected to be less costly than surgery. However, treatment of multiple affected cords may be less costly with surgery compared with multiple Xiapex® injections. The cost-effectiveness of Xiapex® relative to surgery could be enhanced by directing treatment to cases which are expected to demonstrate greater than average efficacy (less severe contractions; MP joints) and at cases which are expected to require fewer injections for successful treatment (e.g. only one or two affected joints).

Xiapex® has not been recommended by the Scottish Medicines Consortium as 'the ... company did not present a sufficiently robust economic analysis'.¹⁸

Treatment with collagenase may be more convenient for patients compared with day-case or in-patient admissions for surgery, particularly as it may be more readily performed on an outpatient basis. However patients will need to attend the following day, and will experience on average two injections and therefore four appointments in total per case.

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Author's declaration: The author has participated in an advisory board regarding a drug which is being jointly marketed in the UK by Pfizer. The author has not participated in any advisory boards or similar regarding Xiapex®, or similar treatments, or any treatment for Dupuytren's contracture, for any party.

Appendix 1. Annual cost of Xiapex® for Dupuytren's contracture based on assumption that one-third of all estimated surgical cases are instead treated with Xiapex®

Primary Care Organisation	Estimated number of surgical cases*	Estimated number of Xiapex® cases (one-third of surgical cases)	Estimated cost of Xiapex® (mean two injections per patient)	Estimated saving against day-case palmar fasciectomy**
NHS Durham & Darlington	148	50	£97,200	£32,400
NHS North of Tyne	191	64	£124,416	£41,500
NHS South of Tyne	160	54	£104,976	£35,000
NHS Tees	126	42	£81,648	£27,200
NHS North East	625	210	£408,240	£136,000

* Excluding revisions and amputations. ** Adjusted to allow for surgical revision in 7% of cases.