

## Re-submission

collagenase clostridium histolyticum 0.9mg powder and solvent for solution  
for injection (Xiapex®) SMC No. (715/11)

Pfizer Ltd.

06 April 2012

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in Scotland. The advice is summarised as follows:

**ADVICE:** following a resubmission

**collagenase clostridium histolyticum (Xiapex®)** is accepted for restricted use within NHS Scotland.

**Indication under review:** treatment of Dupuytren's contracture in adult patients with a palpable cord.

**SMC restriction:** restricted to use as an alternative to limited fasciectomy in adult patients with Dupuytren's contracture of moderate severity (as defined by the British Society for Surgery of the Hand (BSSH), with a palpable cord and up to two affected joints per hand, who are suitable for limited fasciectomy, but for whom percutaneous needle fasciotomy is not considered a suitable treatment option.

Collagenase clostridium histolyticum compared to placebo significantly reduces primary joint contracture in adults with Dupuytren's contracture and palpable cord.

The cost-effectiveness of collagenase clostridium histolyticum relative to percutaneous needle fasciotomy was not demonstrated.

Overleaf is the detailed advice on this product.

**Chairman,  
Scottish Medicines Consortium**

**Indication**

Treatment of Dupuytren's contracture in adult patients with a palpable cord.

**Dosing Information**

0.58mg per injection into a palpable Dupuytren's cord. The volume of reconstituted product to be administered depends on the type of joint being treated as described in the summary of product characteristics. Approximately 24 hours after the injection, a finger extension procedure may be performed, as necessary, to facilitate cord disruption. If a satisfactory response has not been achieved, the injection and finger extension procedures may be repeated after approximately four weeks. Injection 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. If the disease has resulted in multiple contractures, treatment of each cord must be undertaken in a sequential order, as determined by the physician. Clinical study experience with collagenase clostridium histolyticum is currently limited to up to three injections per cord and up to eight injections in total. Collagenase clostridium histolyticum must be administered by a physician appropriately trained in the correct administration of the product and experienced in the diagnosis and management of Dupuytren's disease.

**Product availability date**

01 April 2011

**Summary of evidence on comparative efficacy**

Dupuytren's contracture is a benign proliferative disease that shrinks the connective tissue of the palm and digits, causing the fingers to bend towards the palm. Collagenase clostridium histolyticum (Xiapex®) (hereafter referred to as collagenase) contains two classes of collagenase enzymes that hydrolyse collagen at different sites of the molecule. When injected into a collagen cord, in combination with manipulation, it causes lysis and rupture of the contracted cord, releasing the metacarpo-phalangeal joint (MP) and proximal inter-phalangeal joint (PIP).

The marketing authorisation for collagenase allows up to three injections into each affected cord and the summary of product characteristics notes that clinical experience is limited to up to eight injections. In the case of patients with bilateral disease, it can be used to treat patients with up to two affected joints per hand.

The submitting company has requested that SMC considers the use of collagenase as an alternative to limited fasciectomy in adult patients with Dupuytren's contracture of moderate severity, with a palpable cord and up to two affected joints per hand, who are suitable for limited fasciectomy, but for whom percutaneous needle fasciotomy is not considered a suitable treatment option.

Two similar, 90-day, double-blind studies (CORD I<sup>1</sup> and CORD II<sup>2</sup>) recruited 308 and 66 adults with Dupuytren's contracture of at least one finger (other than the thumb), of 20° to 100° for MP joints or 20° to 80° for PIP joints with a palpable cord and an inability to place affected finger(s) and palm flat against a table. Patients were randomised, with stratification for primary joint type (MP or PIP), severity of primary joint contracture ( $\leq 50^\circ$  or  $>50^\circ$  for MP and  $\leq 40^\circ$  or  $>40^\circ$  for PIP)

in a 1:2 ratio to placebo or collagenase 0.58mg injection to affected cord. In patients whose contracture had not been reduced 24 hours after the injection, joints were manipulated by standard procedure on up to three occasions to try to rupture the cords. Patients were assessed after 30 days and this comprised a treatment cycle. The primary outcome defined as clinical success, was the proportion of primary joints with a reduction in contracture to  $\leq 5^\circ$  of full extension 30 days after the last injection. If the primary joint did not achieve the primary outcome then the affected cord could undergo further treatment cycles up to a maximum of three during the 90-day study.

In CORD II, the primary outcome was assessed in the intention to treat (ITT) population, comprising all patients who received a dose of study drug and in CORD I in a modified ITT population, which excluded patients from the ITT population who did not have fixed-flexion measurements after the first injection or had screening and baseline contracture  $\leq 5^\circ$ . The primary outcome was achieved in significantly more primary joints with collagenase than placebo in CORD II (44% [20/45] versus 4.8% [1/21]) and in CORD I (64% [130/203] versus 6.8% [7/103]). The difference between collagenase and placebo was significant in both studies for the subset of MP joints: 77% (102/133) versus 7.2% (5/69) and 65% (13/20) versus 9.1% (1/11) and in CORD I for the subset of PIP joints: 40% (28/70) versus 5.9% (2/34). In CORD II the difference was not significant for PIP joints: 28% (7/25) versus 0% (0/10). The secondary endpoints of both studies were consistent with results for the primary endpoint in demonstrating benefit of collagenase.

Upon completion of the 90-day double-blind phases, all patients entered an open-label extension phase where they were followed for nine months. Patients who required further treatment because they did not achieve clinical success in the primary joint during the double-blind phase (due to treatment with placebo) or had untreated cords affecting other joints could receive up to five additional injections of collagenase. When the results of both CORD I and CORD II were combined, 50% (264/523) and 51% (68/134) of all joints treated with collagenase during double-blind or open-label phases achieved clinical success 30 days after last injection, with rates for MP joints of 67% (199/299) and 68% (42/62) and for PIP joints of 29% (65/224) and 36% (26/72) respectively. Recurrence was defined as an increase in contracture to at least  $20^\circ$  with the presence of a palpable cord and was evaluated for joints that achieved clinical success during the double-blind and open-label phases. In CORD I, 4.5% (12/264) of joints that achieved clinical success with collagenase during the double-blind or open-label phase had a recurrent contracture, with nine of these in PIP joints. In CORD II, no joints met the criteria for recurrence during either the double-blind or open-label phases.

In an interim two-year analysis from an ongoing five-year follow-up of patients who received collagenase in the two phase III studies described above plus two additional phase III studies, recurrence (defined as an increase in contracture to at least  $20^\circ$  and presence of a palpable cord or the joint required further medical or surgical intervention) was assessed in joints that had achieved clinical success after last injection. Of the 619 joints achieving clinical success, 618 (448 MP and 170 PIP joints) were evaluated to show that 19.3% had recurrence after two years (13.6% for MP and 34.1% for PIP joints). Kaplan-Meier estimates of recurrence at two-years, which censored joints that did not recur at duration of assessment, were 24% (18% for MP and 41% for PIP joints).

A post-hoc sub-group analysis was presented that included data from 58 patients with moderate disease, which represented 16% (58/362) of the study populations of CORD I and CORD II combined. Due to the small patient numbers and different severity of disease profile in the subgroup there were some differences in the patient demographics between the sub-group and

the whole study population. The median total contracture index was lower in the moderate sub-group, 56° compared to 115° and 143° in the CORD I and II populations respectively and the average number of contractures was lower: 1.47 compared to 3.0 and 3.3 in CORD I and II. Analysis of the 57 evaluable joints found that 81% (46/57) of primary joints achieved clinical success after the last collagenase injection, with clinical improvement, defined as >50% reduction from baseline in contracture (flexion deformity) within 30 days of an injection recorded in 88% (50/57) of patients. Results for the total evaluable joints (n=65) in the 58 patients supported the results found for the primary joints. The number of injections per joint did not differ between the sub-group and the total CORD population for both primary joints and all joints groups.

## Summary of evidence on comparative safety

During the double-blind phases of, CORD I and CORD II described above, adverse events were more frequent with collagenase than placebo, with almost all collagenase patients (97% to 100%) reporting a treatment-related adverse event compared with 21% to 38% of placebo-treated patients. However, the majority were mild to moderate and resolved without intervention within a few weeks. The most common adverse events were local injection-site reactions, such as peripheral oedema, contusion, pain and haemorrhage. The majority of patients treated with collagenase developed antibodies to collagenases after one injection and all patients had developed these by their fourth treatment. However, there is no apparent correlation between antibody development and clinical response or adverse reactions. Damage to tendon and ligaments reported as serious adverse events was considered to be due to inadvertent injection of collagenase into these tissues and it is advised that care be taken to only inject the palpable cord.

There was no significant difference in the adverse events profile in the moderately severe subgroup compared to the whole CORD I and II population.

## Summary of clinical effectiveness issues

Dupuytren's contracture can limit hand function and, depending on severity, impact on the patient's ability to work and undertake daily activities. It is a common condition in Northern Europe, and experts have confirmed it is common in Scotland. The British Society of Surgery for the Hand (BSSH) guidance for surgical intervention in Dupuytren's disease states that the disease can be classified as mild, moderate and severe depending on degree of contracture and functional problems. Mild disease requires no treatment. For moderate disease, percutaneous needle fasciotomy (dividing the cord without excision), and possibly collagenase or referral for limited fasciectomy (removal of part of the cord) is recommended, with more extensive fasciectomy (e.g. dermofasciectomy) procedures recommended for severe disease. Both the administration of collagenase and fasciotomy treatments are carried out in an outpatient setting, while fasciectomy requires open surgery with significant recovery time and use of finger splints. None of these procedures is curative and the contracture can recur. The European Medicines Agency (EMA) concluded that recurrence rates with collagenase were broadly similar to surgical intervention and favourable compared with percutaneous needle fasciotomy.<sup>3</sup>

Collagenase is the first pharmacological treatment licensed in the UK for Dupuytren's contracture and provides a non-surgical treatment option for this condition. In both CORD 1 and CORD II, clinical success was significantly more likely with collagenase injection than with placebo for all joints. Patients in whom treatment with collagenase is not successful after one injection can have it repeated after 30 days and again after another 30 days if still unsuccessful. On average, patients have required one or two injections for success. However each finger has to be treated sequentially, so patients with a number of affected joints could require treatment over several months.

The company has requested that SMC considers the use of collagenase as an alternative to limited fasciectomy in adult patients with Dupuytren's contracture of moderate severity, with a palpable cord, and up to two affected joints per hand, who are appropriate for limited fasciectomy, but for whom percutaneous needle fasciotomy is not considered a suitable treatment option. Moderate disease is defined in the BSSH guidelines as notable functional problems, moderate metacarpo-phalangeal joint contracture (30° to 60°), moderate proximal inter-phalangeal joint contracture (<30°), or first web contracture. A post hoc analysis was presented for a subgroup representing patients with moderate disease from the CORD I and II studies. Limitations in this analysis include small patient numbers and differences in baseline demographics due to the exclusion of patients with more severe disease, which result in the total contracture index and the average number of contractures both being significantly lower in the subgroup; this gives rise to uncertainty about the robustness of the observed treatment benefit. The percentage of primary joints achieving the primary outcome of clinical success was higher in the 58 patients identified with moderate disease than for the whole ITT study population. Results demonstrated greater changes both from baseline and versus placebo.

Percutaneous needle fasciotomy is most suitable for less severe disease and for elderly patients unsuitable for surgery. Limited fasciectomy is the most widely used surgical technique but there is a risk of complications. Depending on the intervention, follow-up treatments vary. Collagenase treatment requires initial physiotherapy and daily digital exercises for several months but, if successful, initial recovery is quicker, while surgical treatment with limited fasciectomy requires a number of weeks before full use of the hand is recovered.

There are no direct comparative studies of collagenase versus fasciectomy. The submitting company performed a naïve qualitative indirect comparison of three fasciectomy studies which were identified in a systematic literature review and data from the CORD I and II full study populations (not the subgroup with up to two affected joints and moderate disease). This was used to support the assumption of equivalent efficacy and safety of these treatments, which is pivotal to the cost-minimisation economic analysis. It has a number of limitations, including the small evidence base used for estimating the treatment effect of fasciectomy, and differences or uncertainties between this and the evidence base for collagenase in terms of study inclusion criteria, baseline disease severity and definition, assessment and results for outcomes.

Collagenase offers a non-surgical alternative to limited fasciectomy for patients with moderate disease. A non-surgical option may also lead to more patients receiving treatment for their Dupuytren's contracture. Administration of collagenase requires special training in the technique.

## Summary of comparative health economic evidence

The company submitted a cost-minimisation analysis comparing collagenase with fasciectomy in adults with Dupuytren's contracture. The analysis focused on the use of collagenase as an alternative to fasciectomy as a treatment for Dupuytren's contracture in adult patients with a palpable cord, who have up to two affected joints per hand, who are appropriate for fasciectomy but for whom percutaneous needle fasciotomy is not considered a suitable treatment option, and have moderate severity disease as defined by the BSSH guidelines.

The analysis was conducted over a one-year time horizon in order to capture the cost of one treatment and any follow-up required post-surgery. The clinical data to support the assumption of comparable efficacy with fasciectomy were based on a naïve indirect comparison. The rate of recurrence associated with each treatment was also assumed to be comparable and was therefore not included in the analysis.

Drug acquisition costs, outpatient administration and follow-up visits were included in the collagenase arm. The drug acquisition cost was based on 1.84 injections per patient, which was the mean number of injections administered in the subgroup of patients with moderate disease and up to two affected joints. In the fasciectomy arm, the costs of surgery, follow-up visits and physiotherapy visits post-surgery were included.

The manufacturer estimated that treatment with collagenase would cost £1,723 and fasciectomy would cost £2,498, resulting in savings of £775 per patient. Collagenase was therefore said to be the preferred treatment on cost-minimisation grounds. The sensitivity analysis indicated that collagenase remained cost-saving compared with fasciectomy if patients required fewer than 2.7 injections on average. A threshold analysis which assumed lower efficacy with collagenase indicated that in order for the cost-savings with collagenase to be offset, approximately one third of collagenase patients would have to subsequently require fasciectomy as the result of treatment failure or recurrent disease.

The key issues with the analysis were:

- The assumption of comparable efficacy was based on a naïve qualitative indirect comparison which involved comparing individual arms of the collagenase and fasciectomy trials. The data used in the naïve indirect comparison were not based on the subgroup of patients with two or fewer affected joints or patients with moderate disease. Given the weaknesses of the indirect comparison, the assumption of comparable efficacy which underpins the cost-minimisation analysis is uncertain.
- A comparison with fasciotomy was not included as the company has positioned the use of collagenase in patients who have moderate disease and are not suitable for fasciotomy. As such, the cost-effectiveness of collagenase compared to fasciotomy has not been assessed.

Despite these issues, the economic case was considered demonstrated for the target patient population proposed in the company's submission.

## Summary of patient and public involvement

A Patient Interest Group Submission was received from: British Dupuytren Society.

## Additional information: guidelines and protocols

In February 2004 the National Institute for Health and Clinical Excellence (NICE) issued interventional procedure guidance number 43: needle fasciotomy for Dupuytren's contracture. This recommends that current evidence on the safety and efficacy of needle fasciotomy for Dupuytren's contracture appears adequate to support the use of the procedure, provided that normal arrangements are in place for consent, audit and clinical governance.

In November 2010 NICE issued interventional procedure guidance number 368: radiation therapy for early Dupuytren's disease. This recommends that the evidence on the safety of radiation therapy for early Dupuytren's contracture is limited in quantity but does not raise any serious safety concerns. The evidence on efficacy is limited in quantity and there is uncertainty about the natural history of early Dupuytren's disease, which makes evaluation of the effect of the procedure difficult. Therefore this procedure should only be used with special arrangements for clinical governance, consent and audit or research.

The British Society for Surgery of the Hand (BSSH) has published a guide on Dupuytren's that is intended to inform and guide tertiary referral. This recommends that for mild disease the patient should be reassured and observed; for moderate disease needle fasciotomy can be performed by the physician if appropriately trained, collagenase may possibly be used or the patient should be referred for limited fasciectomy; and for severe disease the patient should be referred for limited fasciectomy or dermofasciectomy.

## Additional information: comparators

The main comparator is fasciectomy, to a lesser extent percutaneous needle fasciotomy and in some patients, no active treatment.

## Cost of relevant comparators

Drug	Dose Regimen	Cost per course (£)
collagenase clostridium histolyticum	One to three intralesional injections over 90 days	650 to 1,950

Costs from eVadis on 13 Feb 2012.

## **Additional information: budget impact**

The submitting company estimated the population eligible for treatment to be 130 patients. Based on an estimated uptake of 16% (21 patients) in year 1 and 80% (104 patients) in year 5, the impact on the medicines budget was estimated at £25k in year 1 and £124k in year 5. As the comparator treatment was fasciectomy the company did not include any savings from displaced medicines.

Feedback from SMC clinical experts suggests that the patient numbers predicted by the submitting company may be an underestimate.

## References

The undernoted references were supplied with the submission. The reference shaded in grey is in addition to those supplied with the submission.

1. Hurst LC, Badalamente MA, Hentz VR et al. Injectable collagenase clostridium histolyticum for Dupuytren's contracture. N Engl J Med. 2009; 361(10): 968-79.
2. Gilpin D, Coleman S, Hall S et al. Injectable Collagenase Clostridium Histolyticum: A New Nonsurgical Treatment for Dupuytren's Disease. J Hand Surg Am 2010; 35(12): 2027-38 e1.
3. European Medicines Agency. Assessment report for Xiapex (collagenase clostridium histolyticum) EMEA/H/C/2048 <http://ema.europa.eu>

This assessment is based on data submitted by the applicant company up to and including **15 March 2012**.

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

### **Advice context:**

*No part of this advice may be used without the whole of the advice being quoted in full.*

*This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.*