Pharmacotherapeutic report, summary

Collagenase *clostridium histolyticum* (Xiapex®) for the indication 'treatment of Dupuytren's contracture with a palpable cord´

Approved on 23 April 2012 by the Medicinal Products Reimbursement Committee (CFH)

Medicine. Collagenase *clostridium histolyticum* powder for solution for injection 0.9 mg; with solvent 3 ml.

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

Posology. The recommended dose is 0.58 mg collagenase *clostridium histolyticum*, dissolved in the solution supplied, by means of intralesional injection in a palpable cord. Only one cord must be treated at a time. Up to 8 injections in total may be administered, up to 3 times per cord at approximately 4-week intervals. Per patient an average of 1.08 injections per joint is needed for clinical success. Most patients have multiple contractures, which demands, on average, two injections per patient.

Mechanism of action. Injection of collagenase into a Dupuytren's cord results in enzymatic disruption of interstitial collagen. The active components of collagenase *clostridium histolyticum* are a mixture of two classes of collagenases with similar but complementary substrate specificity. They cleave interstitial collagen at different sites on the molecule. As a result cleavage occurs at different sites of the collagen fragments.

Particulars. Collagenase is the first pharmacotherapeutic treatment available for Dupuytren's Disease. Up till now only a variety of surgical techniques were used to treat this disorder. Collagenase must be administered by a physician appropriately trained in the administration of the product and experienced in the diagnosis and management of Dupuytren's Disease.

Summary of the therapeutic value

Intended effects. As no studies are available in which collagenase was directly compared with fasciectomy, the only comparison possible is on the basis of an indirect comparison. However, no indirect comparison can be made. No unequivocal, quantitative conclusion can be drawn about the results and efficacy of fasciectomy based on the studies carried out due to large inconsistencies in their set-up and implementation. Furthermore, differences exist in chosen endpoint measures, patient characteristics and follow-up periods between the studies in which fasciectomy and collagenase were studied. Lastly, the collagenase studies provide no information on long-term effects, particularly on an important endpoint measure 'persistence of clinical efficacy'. For this reason the CFH has concluded that it is not possible, based on the current data, to issue a substantiated statement on the favourable effects of collagenase in comparison with fasciectomy.

Unintended effects. No quantitative statement can be made about the unintended effects of injecting collagenase in comparison with fasciectomy due to the lack of comparative studies.

The only qualitative statement that can be made is about the differences in unintended effects. The unintended effects of fasciectomy are symptoms of pain, Complex Regional Pain Syndrome (CPRS), wound-healing problems, hypoesthesia, nerve damage (including neuropraxia) and infection. Collagenase injections often leads to contusion, haematoma and bleeding as well as various skin complaints. The latter are usually temporary and related to the injection site.
The incidence of two severe unintended effects after injection with collagenase, tendon rupture and ligament damage, is low and associated with lack of experience and lack of technique of the administering physician. Physicians' training and knowledge can prevent these unintended effects.

Experience. Experience with collagenase is limited to clinical studies and one year's experience due to the commercial availability of the product Xiapex® in the United States. Ample experience has been gained with fasciectomy, although there is no scientific substantiation for it, nor any agreement about the most effective fasciectomy technique.

Applicability. There are no major differences in applicability between collagenase and fasciectomy for the groups of patients eligible for treatment.

Ease of use. Treatment with collagenase will be less burdensome for patients than fasciectomy, as an injection is less invasive and the recovery period is shorter. The convalescence period is shorter and pain symptoms seem to be of a different nature and not to last as long. The physician's skills and the technique affect the final results with both collagenase injection and fasciectomy.

Final conclusion on therapeutic value.

On the basis of a comparison between collagenase studies and fasciectomy studies, no statement can be issued about the efficacy of collagenase in comparison with (partial) fasciectomy.
An indirect comparison is not possible due to large differences in patient characteristics, endpoint measures and follow-up duration between the various fasciectomy studies.
Furthermore, there is a lack of long-term data on the persistence of the clinical efficacy of collagenase, an important endpoint measure for the treatment of Dupuytren's Disease. Moreover, with respect to the unfavourable effects of collagenase, it is not possible to draw an unequivocal conclusion in comparison with fasciectomy. In comparison with surgical treatment via fasciectomy, the ease of use of collagenase is higher due to administration of an injection instead of a surgical intervention.
Based on the lack of data, the conclusion is that using collagenase *clostridium histolyticum* for the treatment of Dupuytren's contracture with a palpable cord has a lower therapeutic value than fasciectomy.

*The original text of this **CFH-Report** of CVZ was in Dutch. Although great care was taken in translating the text from Dutch to English, the translation may nevertheless have resulted in discrepancies. Rights may only be derived on the basis of the Dutch version of CVZ's CFH-Report.*

Furthermore, CVZ points out that only the summary of this report was translated. A proper understanding of all relevant considerations and facts would require familiarity with the Dutch version of this report, including all appendices.