ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Xiapex 0.9 mg powder and solvent for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial of powder contains 0.9 mg of collagenase *clostridium histolyticum**.

*A formulation of two collagenase enzymes co-expressed and harvested from anaerobic fermentation of a phenotypically selected strain of C*lostridium histolyticum* bacterium.

Excipients with known effect
Sodium injected per joint in the treatment of Dupuytren's contracture:
Metacarpophalangeal (MP) joints: 0.9 mg.
Proximal interphalangeal (PIP) joints: 0.7 mg.

Sodium injected per plaque in the treatment of Peyronie's disease: 0.9 mg.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection.
The powder is a white lyophilised powder.

The solvent is a clear colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Xiapex is indicated for:
- The treatment of Dupuytren's contracture in adult patients with a palpable cord.
- The treatment of adult men with Peyronie's disease with a palpable plaque and curvature deformity of at least 30 degrees at the start of therapy (see sections 4.2 and 4.4).

4.2 Posology and method of administration

Dupuytren's contracture

Xiapex must be administered by a physician appropriately trained in the correct administration of the medicinal product and experienced in the diagnosis and management of Dupuytren's disease.

Posology
The recommended dose of Xiapex is 0.58 mg per injection into a palpable Dupuytren's cord. The volume of solvent required and the volume of reconstituted Xiapex to be administered into the Dupuytren's cord differs depending on the type of joint being treated (for the reconstitution instructions, see section 6.6, Table 14).
- For cords affecting MP joints each dose is administered in an injection volume of 0.25 ml.
- For cords affecting PIP joints, each dose is administered in an injection volume of 0.20 ml.

Injections in up to two cords or two affected joints in the same hand can be administered according to the injection procedure during a treatment visit. Two palpable cords affecting two joints may be injected or one palpable cord affecting two joints in the same finger may be injected at two locations

during a treatment visit. Each injection contains a 0.58 mg dose. If the disease has resulted in multiple contractures, additional cords may be treated at other treatment visits approximately 4 weeks apart.

Approximately 24-72 hours after 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 4 weeks. Injections and finger extension procedures may be administered up to 3 times per cord at approximately 4-week intervals. Clinical study experience with Xiapex is currently limited to up to 3 injections per cord and up to 8 injections in total.

Peyronie's disease

Xiapex must be administered by a physician appropriately trained in the correct administration of the medicinal product and experienced in the diagnosis and treatment of male urological diseases. Patients with penile curvature >90° were not included in the clinical studies. Treatment in this group can therefore not be recommended.

Posology

The recommended dose of Xiapex is 0.58 mg per injection administered into a Peyronie's plaque. The volume of reconstituted Xiapex to be administered into the plaque is 0.25 ml (for reconstitution instructions, see section 6.6, Table 14). If more than one plaque is present, only the plaque causing the curvature deformity should be injected.

A treatment course consists of a maximum of 4 treatment cycles. Each treatment cycle consists of two Xiapex injections and one penile modelling procedure. The second Xiapex injection is administered 1 to 3 days after the first injection. A penile modelling procedure is performed 1 to 3 days after the second injection of each treatment cycle. The interval between treatment cycles is approximately six weeks.

Special population

Elderly

Due to the lack of quantifiable systemic exposure of Xiapex in patients with Dupuytren's contracture and minimal and short-lived systemic exposure of Xiapex in patients with Peyronie's disease, no dose adjustment is necessary. No overall differences in safety or effectiveness were observed between elderly and younger patients.

Hepatic impairment

Due to the lack of quantifiable systemic exposure of Xiapex in patients with Dupuytren's contracture and minimal and short-lived systemic exposure of Xiapex in patients with Peyronie's disease, no dose adjustment is necessary.

Renal impairment

Due to the lack of quantifiable systemic exposure of Xiapex in patients with Dupuytren's contracture and minimal and short-lived systemic exposure of Xiapex in patients with Peyronie's disease, no dose adjustment is necessary.

Paediatric population

There is no relevant use of Xiapex in the paediatric population aged 0-18 years for the treatment of Dupuytren's contracture.

Peyronie's disease occurs exclusively in adult male patients and hence there is no relevant use of Xiapex in the paediatric population aged 0-18 years for the treatment of Peyronie's disease.

Method of administration

Intralesional use.

Xiapex must be reconstituted with the solvent provided and to the appropriate volume prior to intralesional injection (see section 6.6).
A single-use syringe containing 0.01-ml graduations with a permanently fixed 27-gauge 12 or 13 mm needle (not supplied) should be used to withdraw the volume of reconstituted solution. There will be a small amount of reconstituted solution left in the vial.

For instructions on reconstitution of the medicinal product before administration, see section 6.6.

Dupuytren's contracture

Injection procedure
Administration of a local anaesthetic medicinal product prior to injection of Xiapex into a Dupuytren's cord is not recommended, as it may interfere with proper placement of the injection.

The joint to be treated (metacarpophalangeal [MP] or proximal interphalangeal [PIP]) should be confirmed and the volume of solvent required for reconstitution is determined by the type of joint (PIP joint requires a smaller volume for injection). The injection procedure is detailed in the package leaflet and the physician training material and must be followed.

Patients should be instructed:
- To return to see their physician approximately 24-72 hours after injection for an examination of the injected hand and a finger extension procedure to disrupt the cord.
- Not to flex or extend the fingers of the injected hand to reduce extravasation of Xiapex out of the cord until the finger extension procedure is completed.
- Not to attempt to disrupt the injected cord by self-manipulation at any time.
- To elevate the injected hand as much as possible until the day after the finger extension procedure.

Finger extension procedure
At the follow-up visit approximately 24-72 hours after injection, it should be determined if the contracture has resolved. If a cord contracture remains, a passive finger extension procedure will be performed in an attempt to disrupt the cord. Local anaesthesia may be used, if needed, during the finger extension procedure.
While the patient's wrist is in the flexed position, a moderate stretching pressure should be applied to the injected cord by extending the finger for approximately 10 to 20 seconds. For cords affecting the PIP joint, the finger extension procedure should be performed when the MP joint is in the flexed position. If the first finger extension procedure does not result in disruption of the cord, a second and third attempt can be performed at 5- to 10-minute intervals. No more than 3 attempts per affected joint are recommended to disrupt a cord.

If the cord has not disrupted after 3 attempts of extension, a follow-up visit may be scheduled approximately 4 weeks after the injection. If, at that subsequent visit the contracted cord persists, an additional injection and finger extension procedure may be performed.
Following the finger extension procedure(s) and fitting patient with a splint (with treated joint in maximum extension), the patients should be instructed to:
- Not perform strenuous activity with the injected hand until advised to do so.
- Wear the splint at bedtime for up to 4 months.
- Perform a series of finger flexion and extension exercises several times a day for several months.

Peyronie's disease

Injection procedure
Administration of regional anaesthesia (penile block) or topical anaesthesia could be applied prior to Xiapex injection when desired. In the pivotal clinical studies about 30% of the patients received penile block before injection.

The location of the target treatment area in the Peyronie's plaque is identified at the point of maximum concavity (or focal point) in the erect penis state and marked with a surgical marker. Xiapex should be injected into the target plaque when the penis is in a flaccid state. The injection procedure is detailed in the package leaflet and the physician training material and must be followed.

Penile modelling procedure
Penile modelling helps relieve curvature deformity and straighten the penile shaft. At the follow-up visit 1 to 3 days after the second injection of each treatment cycle, the trained physician should perform a penile modelling procedure on the flaccid penis to stretch and elongate the treated plaque that Xiapex has disrupted. Local anaesthesia may be applied before the modelling if desired. Wearing gloves the physician should grasp the plaque or indurated portion of the flaccid penis about 1 cm proximal and distal to the injection site. Direct pressure on the injection site should be avoided. The target plaque is used as a fulcrum point with both hands, to firmly apply a steady pressure to elongate and stretch the plaque. The goal is to gradually create bending opposite to the patient's penile curvature, with stretching to the point of moderate resistance.
The penile pressure should be hold for 30 seconds, thereafter released with a resting period for 30 seconds before repeating the penile modelling technique for a total of 3 modelling attempts at 30 seconds for each attempt.

In addition to the in-office penile modelling procedure, patients should be provided instructions on the appropriate technique to self-perform penile modelling activities at home each day for the 6-week period following the physician penile plaque modelling visit of each treatment cycle, according to the detailed instructions provided in the package leaflet.

If the curvature deformity is less than 15 degrees after the first, second or third treatment cycle, or if the physician determines that further treatment is not clinically indicated, then the subsequent treatment cycles should not be administered.

The safety of more than one treatment course of Xiapex for Peyronie's disease is not known.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Treatment of Peyronie's plaques that involve the penile urethra due to potential risk to this structure.

4.4 Special warnings and precautions for use

Allergic reactions
Following Xiapex injection, severe allergic reaction could occur, and patients should be observed for 30 minutes before leaving the clinic in order to monitor for any signs or symptoms of a serious allergic reaction, e.g. wide spread redness or rash, swelling, tightness in the throat or difficulty breathing. Patients should be instructed to consult a doctor immediately if they experience any of these signs or symptoms. Emergency medication for treatment of potential allergic reactions should be available.

An anaphylactic reaction was reported in a post-marketing clinical study in a patient who had previous exposure to Xiapex for the treatment of Dupuytren's contracture, demonstrating that severe reactions including anaphylaxis can occur following Xiapex injections. Some patients with Dupuytren's contracture developed IgE-anti-drug antibodies in greater proportions and higher titers with successive Xiapex injections.

In the double-blind portion of the three phase 3 placebo-controlled clinical studies in Dupuytren's contracture, 17% of Xiapex-treated patients had mild reactions (i.e. pruritus) after up to 3 injections. The incidence of Xiapex-associated pruritus increased after more Xiapex injections in patients with Dupuytren's contracture.

In the double-blind portion of the two phase 3 placebo-controlled clinical trials in Peyronie's disease, a greater proportion of Xiapex-treated patients (4%) compared to placebo-treated patients (1%) had localized pruritus after up to 4 treatment cycles (involving up to 8 Xiapex injections). The incidence of Xiapex-associated pruritus was similar after each injection regardless of the number of injections administered.

Tendon rupture or other serious injury to the injected finger/hand in the treatment of Dupuytren's contracture

Xiapex must only be injected into the Dupuytren's cord. Because Xiapex lyses collagen, care must be taken to avoid injecting into tendons, nerves, blood vessels, or other collagen-containing structures of the hand. Injection of Xiapex into collagen containing structures may result in damage to those structures, and possible permanent injury such as tendon rupture or ligament damage. Care should be taken when injecting Xiapex into cords contracting the PIP joints as clinical studies indicate an increased risk of tendon rupture and ligament injury associated with treatment of PIP contractures with Xiapex. This is particularly important for cords situated at the PIP joint of the fifth finger. When injecting a cord affecting a PIP joint of the fifth finger, the needle insertion must not be more than 2 to 3 mm in depth and not more than 4 mm distal to the palmar digital crease. Patients should be instructed to comply with the treatment instructions (see section 4.2) and to promptly contact the physician if there is trouble bending the finger after the swelling goes down (symptoms of tendon rupture).

Most patients experiencing tendon/ligament rupture or injury have gone on to have successful surgical repair. Early diagnosis and prompt evaluation and treatment are important because tendon rupture/ligament injury may potentially affect overall hand function.

Patients with Dupuytren's contractures that adhere to the skin may be at higher risk of skin lesions as a result of the pharmacological effect of Xiapex and the finger extension procedure on the skin overlying the targeted cord.

Cases of skin laceration requiring skin graft after finger extension procedures have been reported post-marketing. Signs or symptoms that may reflect serious injury to the treated finger/hand after injection or manipulation should be promptly evaluated because surgical intervention may be required. A higher rate for skin laceration has been shown following two concurrent injections in the same hand in a controlled post-marketing trial (see also Section 4.8).

Cases of finger necrosis have been reported, which in some cases led to amputation of finger parts. Pre-existing reduced peripheral circulation, e.g. Raynaud syndrome, and the use of epinephrine combined with local anaesthetics in these patients may contribute to this (see also section 4.8).

Cases of digital phalangeal fractures have been reported after finger manipulation procedure. Caution should be exercised when performing finger extension procedures in patients with bone fragility, which may predispose to digital phalangeal fracture (e.g. in patients with osteopenia/osteoporosis). Diagnostic imaging is recommended after manipulation if finger deformity, pain or increased swelling develops (see also section 4.8).

Corporal rupture (fracture of penis) or other serious injury to the penis in the treatment of Peyronie's disease

Injection of Xiapex into collagen-containing structures such as the corpora cavernosa of the penis may result in damage to those structures and possible injury such as corporal rupture (penile fracture). Therefore, Xiapex must be injected only into the Peyronie's plaque and care should be taken to avoid injecting into the urethra, nerves, blood vessels, corpora cavernosa or other collagen-containing structures of the penis.

Corporal rupture was reported as a serious adverse reaction after Xiapex injection in 5 out of 1044 patients (0.5%) in the controlled and uncontrolled clinical trials in Peyronie's disease. In other Xiapex-treated patients (9 of 1044; 0.9%), a combination of penile ecchymoses or haematoma, sudden

penile detumescence, and/or a penile "popping" sound or sensation was reported, and in these cases, a diagnosis of corporal rupture cannot be excluded.

Severe penile haematoma was also reported as an adverse reaction in 39 of 1044 patients (3.7%) in the controlled and uncontrolled clinical studies in Peyronie's disease.

Physicians should advise the patient to wait for at least 4 weeks after the second injection of a treatment cycle before resuming sexual activity taking care to ensure that any pain and swelling has ceased and to be cautious when resuming sexual activity.

Signs or symptoms that may reflect serious injury to the penis should be promptly evaluated in order to assess for corporal rupture or severe penile haematoma, which may require surgical intervention.

Use in patients with coagulation disorders

Xiapex must be used with caution in patients with coagulation disorders or those taking anticoagulants. In the three double-blind, placebo-controlled phase 3 studies in Dupuytren's contracture, 73% of Xiapex-treated patients reported an ecchymosis or a contusion and 38% reported a haemorrhage at the injection site. In the two double-blind, placebo-controlled phase 3 studies in Peyronie's disease, 65.5% of Xiapex-treated patients developed penile haematoma and 14.5% developed penile ecchymosis. The efficacy and safety of Xiapex in patients receiving anticoagulant medicinal products other than up to 150 mg acetylsalicylic acid per day prior to Xiapex administration is not known. Use of Xiapex in patients who have received anticoagulants (with the exception of up to 150 mg acetylsalicylic acid daily) within 7 days prior to receiving an injection of Xiapex is not recommended.

Immunogenicity

As with any non-human protein medicinal product, patients may develop antibodies to the therapeutic protein. During clinical studies, blood samples from patients with Dupuytren's contracture and Peyronie's disease were tested at multiple time points for antibodies to the protein components of the medicinal product (AUX-I and AUX-II).

In the Dupuytren's contracture clinical trials at 30 days post the first injection, 92% of patients had circulating antibodies detected against AUX-I and 86% of patients against AUX-II. At five years after the initial injection of Xiapex, 92.8% and 93.4% of subjects were seropositive for anti-AUX-I and anti-AUX-II respectively.

Almost all patients had positive titers for anti-AUX-I antibodies (97.9%) and anti-AUX-II antibodies (97.5%) 60 days post two concurrent injections.

In the Peyronie's disease clinical studies, at 6 weeks after the first treatment cycle of Xiapex, approximately 75% of patients had antibodies against AUX-I and approximately 55% of patients had antibodies against AUX-II. Six weeks after the eighth injection (fourth treatment cycle) of Xiapex >99% of Xiapex-treated patients developed high titers of antibodies to both AUX-I and AUX-II. Neutralizing antibodies were assayed for a subset of 70 samples selected to be representative of high and low titer binding antibody responses at week 12 of treatment. For each subject in whom a Week 12 sample was selected, the corresponding Week 6, 18, 24, and 52 samples were assayed if they were also binding antibody positive. Neutralizing antibodies to AUX-I or AUX-II, were detected in 60% and 51.8%, respectively, of patients tested. At five years after the initial injection of Xiapex the majority of subjects (>90%) were seropositive for anti-AUX-I and anti-AUX-II antibodies. In addition, seropositivity for neutralizing anti-AUX-I and anti-AUX-II antibodies was maintained.

In patients treated for these two indications, there was no apparent correlation of antibody frequency, antibody titers, or neutralizing status to clinical response or adverse reactions.

Since the enzymes in Xiapex have some sequence homology with human matrix metalloproteinases (MMPs), anti-drug antibodies (ADA) could theoretically interfere with human MMPs. No safety concerns related to the inhibition of endogenous MMPs have been observed, in particular no adverse

events indicating the development or exacerbation of autoimmune diseases or the development of a musculoskeletal syndrome (MSS). Whilst there is no clinical evidence from the current safety data of a musculoskeletal syndrome developing following the administration of Xiapex, the potential for it to occur cannot be excluded. If this syndrome were to develop, it would occur progressively and is characterized by one or more of the following signs and symptoms: arthralgia, myalgia, joint stiffness, stiffness of the shoulders, hand oedema, palmar fibrosis and thickening or nodules forming in the tendons.

Post-treatment surgery
The impact of treatment with Xiapex on subsequent surgery, if needed, is not known.

Special penile conditions/diseases not studied in clinical trials
Xiapex treatment in patients having a calcified plaque that could have interfered with the injection technique, chordee in the presence or absence of hypospadias, thrombosis of the dorsal penile artery and/or vein, infiltration by a benign or malignant mass resulting in penile curvature, infiltration by an infectious agent, such as in lymphogranuloma venereum, ventral curvature from any cause and isolated hourglass deformity of the penis has not been studied and treatment in these patients should be avoided.

Excipients
This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium- free'.

4.5 Interaction with other medicinal products and other forms of interaction

No formal medicinal product interaction studies with Xiapex have been performed. There is no quantifiable systemic exposure following a single injection of Xiapex in patients with Dupuytren's contracture and only minimal and short-lived systemic exposure of Xiapex in patients with Peyronie's disease.

There were no clinically meaningful differences in the incidence of adverse events following treatment with Xiapex based on the severity of baseline erectile dysfunction or concomitant phosphodiesterase type 5 (PDE5) inhibitor use.

Whilst there is no clinical evidence of an interaction between tetracycline and anthracycline/anthraquinolone antibiotics and anthraquinone derivatives and Xiapex, such derivatives have been shown to inhibit matrix metalloproteinase-mediated collagen degradation at pharmacologically relevant concentrations *in vitro*. Therefore, use of Xiapex in patients who have received tetracycline antibiotics (e.g., doxycycline) within 14 days prior to receiving an injection of Xiapex is not recommended.

4.6 Fertility, pregnancy and lactation

Pregnancy and fertility
For Xiapex no clinical data on exposed pregnancies are available. Animal studies do not indicate direct or indirect harmful effects with respect to fertility, pregnancy, or embryonal/foetal development, (see section 5.3). Parturition or postnatal development studies in animals were not conducted since human pharmacokinetic studies show that Xiapex levels are not quantifiable in the systemic circulation following injection into a Dupuytren's cord (see section 5.1). Patients develop ADAs after repeated administration, the cross-reactivity of which versus endogenous MMPs involved in pregnancy and labour cannot be excluded. The potential risk for humans on parturition and postnatal development is unknown. Therefore, the use of Xiapex is not recommended in pregnancy and treatment should be postponed until after pregnancy.

Peyronie's disease occurs exclusively in adult male patients and hence there is no relevant information for use in females. Low levels of Xiapex were quantifiable in the plasma of evaluable male patients for

up to 30 minutes following administration of Xiapex into the penile plaque of patients with Peyronie's disease (see section 5.2).

Breast-feeding
It is not known whether collagenase *clostridium histolyticum* is excreted in human milk. Caution should be exercised when Xiapex is administered to a breast-feeding woman.

4.7 Effects on ability to drive and use machines

Xiapex may have a major influence on the ability to drive and use machines due to the swelling and pain which may impair the use of the treated hand in Dupuytren's disease. Other minor influences on the ability to drive and use machines include dizziness, paresthesia, hypoesthesia, and headache that have also been reported following injection of Xiapex. Patients must be instructed to avoid potentially hazardous tasks such as driving or using machines until it is safe to do so or as advised by the physician.

4.8 Undesirable effects

Dupuytren's contracture

Summary of the safety profile
The most frequently reported adverse reactions during the Xiapex clinical studies (272 of 409 patients received up to three single injections of Xiapex and 775 patients received two concurrent injections in the same hand) were local injection site reactions such as oedema peripheral (local to the injection site), contusion (including ecchymosis), injection site haemorrhage and injection site pain. Injection site reactions were very common, occurring in the vast majority of patients, were mostly mild to moderate in severity and generally subsided within 1-2 weeks post injection. Serious adverse reactions of tendon rupture (6 cases), tendonitis (1 case), other ligament injury (2 cases) and complex regional pain syndrome (1 case) related to the medicinal product were reported. Anaphylactic reaction was reported in a patient previously treated with Xiapex (1 case).

Tabulated list of adverse reactions
Table 1 presents adverse reactions listed by system organ class and frequency categories, using the following convention: very common (≥1/10), common (≥1/100 to <1/10), and uncommon (≥1/1,000 to <1/100), and not known: cannot be estimated from the available data. Within each frequency group, adverse reactions are presented in order of decreasing seriousness. Adverse reactions reported from the clinical programme are those that occurred in the Phase 3 double blind placebo-controlled studies for the treatment of Dupuytren's contracture in adult patients with a palpable cord (AUX-CC-857, AUX-CC-859) and the post-marketing clinical studies (AUX-CC-864, AUX-CC-867) for two concurrent injections in the same hand.

Table 1: Tabulated list of adverse reactions.

System organ class	Very common	Common	Uncommon	Not known
Infections and infestations			Injection site cellulitis Lymphangitis	
Blood and lymphatic system disorders	Lymphadenopathy	Lymph node pain	Thrombocytopenia Lymphadenitis	
Immune system disorders			Hypersensitivity Anaphylactic reaction	

System organ class	Very common	Common	Uncommon	Not known
Psychiatric disorders			Disorientation Agitation Insomnia Irritability Restlessness	
Nervous system disorders		Paresthesia Hypoesthesia Burning sensation Dizziness Headache	Complex regional pain syndrome Monoplegia Syncope vasovagal Tremor Hyperaesthesia	
Eye disorders			Eyelid oedema	
Vascular disorders			Haematoma Hypotension	
Respiratory, thoracic and mediastinal disorders			Dyspnoea Hyperventilation	
Gastrointestinal disorders		Nausea	Diarrhoea Vomiting Abdominal pain upper	
Skin and subcutaneous tissue disorders	Pruritus Ecchymosis	Blood blister[a] Blister Rash Erythema Hyperhidrosis	Erythematous or macular rash Eczema Swelling face Skin disorders, like exfoliation, lesions, pain, tightness, discoloration or scab	
Musculoskeletal and connective tissue disorders	Pain in extremity	Arthralgia Axillary mass Joint swelling Myalgia	Pain in chest wall, groin, neck or shoulder Musculoskeletal discomfort or stiffness, joint stiffness or crepitation Limb discomfort Tendonitis Muscle spasms or weakness	
Reproductive system and breast disorders			Breast tenderness Hypertrophy breast	

System organ class	Very common	Common	Uncommon	Not known
General disorders and administration site conditions	Oedema peripheral[c] Injection site haemorrhage, pain or swelling Tenderness	Axillary pain Inflammation Injection site warmth, erythema, inflammation, vesicles or pruritus Swelling	Local swelling Pyrexia Pain Discomfort Fatigue Feeling hot Influenza like illness Injection site reaction, malaise, irritation, anaesthesia, desquamation, nodule or discoloration Cold intolerance of the treated fingers	
Investigations			Lymph node palpable Alanine aminotransferase increased Aspartate aminotransferase increased Body temperature increased	
Injury, poisoning and procedural complications	Contusion	Skin laceration[a,b]	Tendon rupture Ligament injury Limb injury Open wound Wound dehiscence	Digital necrosis[d] Digital fracture[d]

a reported with a higher incidence (very common) in patients who received two concurrent injections of Xiapex in the same hand compared with subjects treated with up to three single injections in the Phase 3 placebo-controlled pivotal studies in Dupuytren's contracture.
b "skin laceration" includes "injection site laceration" and "laceration"
c "oedema peripheral" includes "injection site oedema" and "oedema"
d see also section 4.4

The incidence of skin laceration (29.1%) was higher for subjects treated with two concurrent injections of Xiapex in historically-controlled clinical study AUX-CC-867 compared with subjects treated with up to three single injections in the Phase 3 placebo-controlled pivotal studies in Dupuytren's contracture (CORD I and CORD II) (8.8%). The majority of the skin lacerations occurred on the manipulation day. A higher incidence of skin laceration may be attributable to more vigorous finger extension procedures in patients after receiving anaesthesia to the hand. In Study AUX-CC-867, most (85%) subjects received local anaesthesia prior to the finger extension procedure.
There were no other clinically relevant differences between two concurrent injections of Xiapex in the same hand and up to three single injections of Xiapex in the types of adverse events reported (i.e., most adverse events were local to the treated extremity and of mild or moderate intensity).

The overall safety profile was similar regardless of the timing of the post-injection finger extension procedure (i.e., 24 hours, 48 hours, and ≥72 hours after injection) among patients who received two concurrent injections of Xiapex in Study AUX-CC-867.

Peyronie's disease

Summary of the safety profile
The overall safety profile was similar in the two Phase 3 double-blind placebo-controlled studies (832 male patients, 551 patients received Xiapex) and in an open-label Phase 3 study (189 male patients) of patients who had previously received placebo in the controlled studies. In the two Phase 3 double-blind placebo-controlled studies, most adverse reactions were local events of the penis and groin and the majority of these events were of mild or moderate severity, and most (79%) resolved within 14 days of the injection. The adverse reaction profile was similar after each injection, regardless of the number of injections administered. The most frequently reported adverse drug reactions (≥25%) during the Xiapex controlled clinical studies were penile haematoma, penile swelling and penile pain. Severe penile haematoma including severe injection site haematoma were reported with the frequency very common.

In the controlled and uncontrolled clinical studies of Xiapex in Peyronie's disease corporal rupture and other serious penile injury were reported uncommonly (see section 4.4)

A popping noise or popping sensation in the penis, sometimes described as "snapping" or "cracking" and sometimes accompanied by detumescence, haematoma and/or pain, were reported in 73/551 (13.2%) Xiapex-treated patients and 1/281 (0.3%) placebo-treated patients, in Studies 1 and 2 combined.

Tabulated list of adverse reactions
Table 2 presents adverse reactions listed by system organ class and frequency categories, using the following convention: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), and not known: cannot be estimated from the available data. Within each frequency group, adverse reactions are presented in order of decreasing seriousness. Adverse reactions reported from the clinical programme are those that occurred in the Phase 3 double-blind placebo-controlled studies.

Table 2: Tabulated list of adverse reactions.

System organ class	Very common	Common	Uncommon
Infections and infestations			Fungal skin infection Infection Upper respiratory infection
Blood and lymphatic system disorders			Lymph node pain Eosinophilia Lymphadenopathy
Immune system disorders			Drug hypersensitivity Anaphylactic reaction*
Metabolism and nutrition disorders			Fluid retention
Psychiatric disorders			Abnormal dreams Depression Sexual inhibition
Nervous system disorders			Headache Dizziness Dysgeusia Paraesthesia Burning sensation Hyperaesthesia Hypoaesthesia

System organ class	Very common	Common	Uncommon
Ear and labyrinth disorders			Tinnitus
Cardiac disorders			Tachycardia
Vascular disorders			Haematoma Hypertension Haemorrhage Lymphangiopathy Thrombophlebitis superficial
Respiratory, thoracic and mediastinal disorders			Cough
Gastrointestinal disorders			Abdominal distension Constipation
Skin and subcutaneous tissue disorders		Blood blister Skin discolouration	Erythema Penile ulceration Rash erythematous Night sweats Skin disorder, nodule, granuloma, blister, irritation or oedema Pigmentation disorder Skin hyperpigmentation
Musculoskeletal and connective tissue disorders			Back, pubic or groin pain Ligament disorder Ligament pain Musculoskeletal discomfort
Renal and urinary disorders			Dysuria Micturition urgency
Reproductive system and breast disorders	Penile haematoma[a], swelling[b], pain[c] or ecchymosis[d]	Penile blister Pruritus genital Painful erection Erectile dysfunction Dyspareunia Penile erythema	Penile adhesion Penis disorder Progression of Peyronie's disease Sexual dysfunction Scrotal erythema Genital discomfort Genital haemorrhage Pelvic pain Penile size reduced Penile vein thrombosis Scrotal oedema Scrotal pain

System organ class	Very common	Common	Uncommon
General disorders and administration site conditions		Injection site vesicles or pruritus Localised oedema Nodule Suprapubic pain	Feeling hot Injection site reaction or discolouration Pyrexia Swelling Asthenia Chills Cyst Induration Influenza like illness Oedema Secretion discharge Tenderness
Investigations			Blood glucose increased Blood pressure systolic increased Body temperature increased
Injury, poisoning and procedural complications		Procedural pain	Fracture of penis Skin laceration Open wound Scrotal haematoma Joint injury Penis injury

a Includes: injection site haematoma and penile haematoma were reported with the verbatim term of penile bruising or injection site bruising in 87% of patients.
b Includes: injection site swelling, penile oedema, penile swelling, local swelling, scrotal swelling, and injection site oedema.
c Includes: injection site pain, penile pain, and injection site discomfort.
d Includes: contusion, ecchymosis, penile haemorrhage, and injection site haemorrhage.
∗ reported from a post-marketing clinical study in a patient who had previous exposure to Xiapex for the treatment of Dupuytren's contracture.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Administration of Xiapex at greater than recommended doses is expected to be associated with increased local reactions at the site of injection. Routine supportive care and symptomatic treatment must be provided in the case of overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other Drugs For Disorders of the Musculo-Skeletal System-Enzymes, ATC code: M09AB02

Xiapex is a lyophilized product for parenteral administration containing collagenase *clostridium histolyticum* which is comprised of two collagenases in a defined mass ratio. These collagenases, referred to as AUX-I and AUX-II, are representative of the two major collagenase classes (Class I and

Class II) produced by *Clostridium histolyticum.* AUX-I and AUX-II are single polypeptide chains consisting of approximately 1000 amino acids of known sequence with a molecular weight of 114 kDa and 113 kDa respectively as determined by mass spectrometry. The two polypeptides are purified by chromatographic steps customary for the separation and isolation of biotherapeutic proteins to yield a consistent, well characterized and controlled mixture of two collagenase enzymes.

Because the collagen lysis process following Xiapex administration is localized and does not require or result in quantifiable systemic levels of AUX-I and AUX-II, the primary pharmacodynamic activity of Xiapex cannot be evaluated in subjects and therefore, such studies have not been undertaken.

Mechanism of action

Collagenases are proteinases that hydrolyze collagen under physiological conditions. Xiapex is comprised of a mixture of Class I (AUX-I) and Class II (AUX-II) clostridial collagenases in a defined mass ratio. The two classes of collagenases have similar but complementary substrate specificity. Both collagenases effectively cleave interstitial collagen but at different sites on the molecule; additionally, they prefer different conformations (triple helical versus denatured or cleaved). These differences account for the ability of the two classes of enzymes to digest collagen in a complementary manner. Class I collagenases (α, β, γ, and η) are the products of the *colG* gene, they initiate collagen hydrolysis near the amino and carboxy termini of triple helical domains and generate large proteolytic fragments. In contrast, the Class II collagenases (δ, ε, and ζ,) are products of *colH* gene, their initial cleavage sites are located within the interior of the collagen molecule and generate smaller collagen fragments. Both classes of collagenases readily hydrolyze gelatin (denatured collagen) and small collagen peptides, whereas Class II has higher affinity for small collagen fragments. Class I cleaves insoluble triple helical collagen with higher affinity than Class II collagenase. Together, these collagenases work to provide broad hydrolytic activity towards collagen.

Dupuytren's contracture

Injection of Xiapex into a Dupuytren's cord, which is comprised mostly of interstitial collagen types I and III, results in enzymatic disruption of the cord.

Peyronie's disease

The signs and symptoms of Peyronie's disease are caused by a collagen plaque. Injection of Xiapex into a Peyronie's plaque, which is comprised mostly of collagen, may result in enzymatic disruption of the plaque. Following this disruption of the plaque, penile curvature deformity and patient bother caused by Peyronie's disease are reduced.

Clinical efficacy and safety

Dupuytren's contracture

The efficacy of Xiapex 0.58 mg was evaluated in two pivotal randomized, double-blind, placebo-controlled studies, CORD I (AUX-CC-857) and CORD II (AUX-CC-859), in adult patients with Dupuytren's contracture. The double-blind study population comprised 409 patients of whom 272 received Xiapex 0.58 mg and 137 received placebo. The mean age was 63 years (range 33 to 89 years) and 80% of patients were male. At study entry, patients in the clinical studies had: (1) a finger flexion contracture with a palpable cord of at least one finger (other than the thumb) of 20° to 100° in a MP joint or 20° to 80° in PIP joint and (2) a positive "table top test" defined as the inability to simultaneously place the affected finger(s) and palm flat against a table top. The cord affecting a selected primary joint received up to 3 injections of 0.58 mg of Xiapex or placebo. A finger extension procedure was performed if needed, approximately 24 hours after injection to facilitate disruption of the cord. Each injection was separated by approximately 4 weeks.

The primary endpoint of each study was to evaluate the proportion of patients who achieved a reduction in contracture of the selected primary joint (MP or PIP) to 5° or less of normal, approximately 4 weeks after the last injection of that joint. Other endpoints included ≥50% reduction from baseline in degree of contracture, percent change from baseline in degree of contracture, change from baseline in range of motion, subject global assessment of treatment satisfaction and physician global assessment of severity.

Xiapex demonstrated a clinically significant benefit compared to placebo in the proportion of patients achieving the primary endpoint of a reduction in the contracture of all joints treated to 5° or less, approximately 4 weeks after the last injection (MP plus PIP, MP only, PIP only). For patients who achieved a contracture of the selected joint to 5° or less, the mean number of injections required to achieve this was 1.5 in the 2 studies. Xiapex also demonstrated a clinically significant benefit compared to placebo in decreasing the degree of contracture and increasing both the range of motion from baseline for all joints treated (MP plus PIP, MP only, PIP only) and the subject global assessment of treatment satisfaction.

Table 3 provides demographic and baseline characteristics for the study population and Tables 4-5 provide the results of the major efficacy endpoints measured in the 2 double-blind placebo-controlled studies CORD I (AUX-CC-857) and CORD II (AUX-CC-859).

Table 3.
Demographic and baseline characteristics
Phase 3 Double-Blind, Placebo controlled studies (CORD I, CORD II)

VARIABLE	Xiapex (N=249)	Placebo (N=125)
Age (years)		
Mean	62.7	64.2
Age category (years), n (%)		
< 45	9 (3.6)	5 (4.0)
45 – 54	33 (13.2)	17 (13.6)
55 – 64	103 (41.4)	44 (35.2)
65 – 74	82 (33.0)	40 (32.0)
≥ 75	22 (8.8)	19 (15.2)
Gender, n (%)		
Male	210 (84.3)	91 (72.8)
Female	39 (15.7)	34 (27.2)
Family history of Dupuytren's disease, n (%)		
Yes	107 (43.0)	62 (49.6)
No	142 (57.0)	63 (50.4)
Physician Rating of Severity at Baseline		
Mild	38 (15.4 %)	21 (16.8 %)
Moderate	148 (59.9 %)	71 (56.8 %)
Severe	61 (24.7 %)	33 (26.4 %)
Missing[1]	2 (0.8 %)	-

Note: Includes all patients who received at least 1 injection of double-blind study medicinal product (Xiapex 0.58 mg or placebo).
[1] Not used to calculate physician rating of severity at baseline percentage-actual denominator of N=247 used.

Table 4.
Percentage of patients who achieved reduction in contracture to 5° or less (Last injection)

TREATED PRIMARY JOINTS	CORD I		CORD II	
	Xiapex	Placebo	Xiapex	Placebo
	N=203[c]	N=103[c]	N=45	N=21
All Joints	64.0 %	6.8 %	44.4 %	4.8 %
p-value	<0.001	-	<0.001	-
	N=133	N=69	N=20	N=11
MP Joints[a]	76.7 %	7.2 %	65.0 %	9.1 %
p-value	<0.001	-	0.003	-
	N=70	N=34	N=25	N=10
PIP Joints[b]	40.0 %	5.9 %	28.0 %	0.0 %
p-value	<0.001	-	0.069	-

[a] Metacarpophalangeal joint; [b] Proximal interphalangeal joint; [c] 2 primary joints were excluded from the efficacy analysis (1 joint from the placebo group was not evaluated and 1 joint from the Xiapex treated group had a baseline contracture of 0 degrees before treatment).

Table 5.
Mean increase in range of motion from baseline (Last injection)

TREATED PRIMARY JOINTS	CORD I		CORD II	
	Xiapex	Placebo	Xiapex	Placebo
All Joints	N=203 [c]	N=103 [c]	N=45	N=21
Mean Baseline (SD)	43.9 (20.1)	45.3 (18.7)	40.3 (15.2)	44.0 (16.5)
Mean Final (SD)	80.7 (19.0)	49.5 (22.1)	75.8 (17.7)	51.7 (19.6)
Mean increase (SD)	36.7 (21.0)	4.0 (14.8)	35.4 (17.8)	7.6 (14.9)
MP Joints[a]	N=133	N=69	N=20	N=11
Mean Baseline (SD)	42.6 (20.0)	45.7 (19.2)	39.5 (11.8)	41.4 (20.8)
Mean Final (SD)	83.7 (15.7)	49.7 (21.1)	79.5 (11.1)	50.0 (21.5)
Mean increase (SD)	40.6 (20.0)	3.7 (12.6)	40.0 (13.5)	8.6 (14.7)
PIP Joints[b]	N=70	N=34	N=25	N=10
Mean Baseline (SD)	46.4 (20.4)	44.4 (17.9)	41.0 (17.7)	47.0 (10.3)
Mean Final (SD)	74.9 (23.1)	49.1 (24.4)	72.8 (21.3)	53.5 (18.3)
Mean increase (SD)	29.0 (20.9)	4.7 (18.5)	31.8 (20.1)	6.5 (15.8)

[a] Metacarpophalangeal joint; [b] Proximal interphalangeal joint; [c] 2 primary joints were excluded from the efficacy analysis (1 joint from the placebo group was not evaluated and 1 joint from the Xiapex treated group had a baseline contracture of 0 degrees before treatment).

All p-values < 0.001 for all comparisons between Xiapex and placebo, except for PIP joints in Study CORD II which was not eligible for statistical testing due to a hierarchical testing procedure.

Physician-rated change in contracture severity was reported as very much improved or much improved in 86% and 80% of the subjects in the Xiapex group compared to 3% and 5% of subjects in the placebo group for the CORD I and CORD II studies, respectively (p<0.001). Based on the Patient Global Assessment of Treatment Satisfaction, more than 85% of subjects in the CORD I and CORD II studies reported either being quite satisfied or very satisfied with their treatment with Xiapex versus approximately 30% treated with placebo (p<0.001). Greater patient satisfaction was correlated with improved range of motion (r=0.51, p<0.001).

Treatment of two concurrent injections

The administration of two concurrent Xiapex injections into Dupuytren's cords in the same hand was evaluated in clinical study AUX-CC-867, a historically-controlled, open-label multi-centre trial in 715 adult subjects (1450 Xiapex injections) with Dupuytren's contracture. The finger extension procedures were performed approximately 24 to 72 hours after injection.

Primary efficacy endpoint was fixed flexion contracture in the treated joint pair subgroup. A significant mean improvement (74.4%) from baseline to Day 31 was observed overall in fixed flexion contracture following administration of two concurrent injections of Xiapex 0.58 mg (one injection per joint) in the same hand, see Table 6.

Improvement was observed regardless of joint type or finger involvement (range: 60.5% to 83.9%). Improvement of the total fixed flexion contracture was also observed irrespectively of the time of finger extension, 24, 48 or 72 hours after injection, with a mean improvement at Day 31 of 75.2% 74.8% and 72.4% respectively. An improvement from baseline was also seen in range of motion at Day 31 for all the treated joint pair subgroups, see Table 6.

Table 6.
Total fixed flexion contracture and range of motion following administration of two concurrent injections of Xiapex 0.58 mg in the same hand, mITT population, study AUX-CC-867 (first treatment cycle)

	Same Finger, 1 MP, 1 PIP (n=350)	**Different Fingers, Both MPs (n=244)**	**Different Fingers, Both PIPs (n=72)**	**Different Fingers, 1 MP, 1 PIP (n=58)**	**Total (n=724)**
Total FFC (°)					
Baseline, mean (SD)	102 (31)	89 (31)	109 (37)	96 (28)	98 (32)
Day 31, mean (SD)	30 (27)	17 (28)	47 (39)	31 (29)	27 (30)
Change, mean (SD)	72 (29)	72 (29)	62 (32)	65 (34)	70 (30)
% Change, mean (SD)	72 (22)	84 (23)	60 (29)	68 (27)	74 (25)
Total ROM (°)					
Baseline, mean (SD)	87 (31)	92 (34)	93 (36)	92 (29)	90 (33)
Day 31, mean (SD)	154 (29)	163 (30)	148 (42)	155 (31)	156 (31)
Change, mean (SD)	67 (30)	71 (34)	55 (28)	63 (37)	67 (32)

FFC = Fixed flexion contracture
ROM = Range of motion

Clinical success (a reduction of contracture to ≤5° within 30 days) after two concurrent injections of Xiapex (one per joint) in the same hand was achieved for the majority of MP joints (64.6%) compared with 28.6% of PIP joints following a single injection per affected joint. Time of finger extension after injection had no impact on the rate of clinical success for either MP or PIP joints. Clinically meaningful improvement in hand function as determined by the URAM (Unite´ Rhumatologique des Affections de la Main) score was observed at Day 31 (-11.3) and Day 61 (-12.3).

Long-term efficacy and safety

A long-term, non-treatment, Year 2 to Year 5 follow-up study (AUX-CC-860) was undertaken to evaluate recurrence of contracture and long-term safety in subjects who received up to 8 single injections of Xiapex 0.58 mg in a previous Phase 3 open-label or double-blind with open-label extension study. No new safety signals were identified among subjects who were followed for 5 years after their initial injection of Xiapex in a previous clinical study. The majority of adverse events reported during the long-term follow-up period were non-serious, mild or moderate in intensity, and were not related to the local administration of Xiapex. These data support the long-term safety profile of Xiapex confirming that no new safety risks were identified during the 5 year follow-up period.

Recurrence was assessed in successfully treated joints (i.e., subjects had a reduction in contracture to 5° or less at the Day 30 evaluation after the last injection of Xiapex in a previous study) and was

defined as an increase in joint contracture by at least 20° in the presence of a palpable cord, or the joint underwent medical or surgical intervention primarily to correct a new or worsening Dupuytren's contracture in that joint. Data on the long-term recurrence rates following successful treatment with Xiapex are provided in Table 7.

Table 7.
Long Term Recurrence Rates for Joints Treated Successfully with XIAPEX

Follow-up Interval (days)	N (%) of Joints in Each Interval[a]	N (%) of Recurrent Joints in Each Interval[b]	Cumulative Nominal Recurrence by Joint Type (%)		Cumulative Nominal Recurrence Rate (%)[c]	Nominal Change in Recurrence Rate vs Previous Year (%)
			MP	PIP		
0-365	20 (3.2)	19 (6.3)	1.8	6.4	3.0	-
366-730	114 (18.3)	103 (33.9)	14.2	33.7	19.6	16.6
731-1095	125 (20.1)	97 (31.9)	27.1	56.4	35.2	15.6
1096-1460	85 (13.6)	45 (14.8)	34.8	62.2	42.4	7.2
1461-1825	169 (27.1)	27 (8.9)	39.5	65.7	46.7	4.3
> 1825	110 (17.7)	13 (4.3)	41.9	66.9	48.8	2.1

a A joint was considered in an interval if the duration of assessment falls in the interval. The duration of assessment started at the day of success (visit after the last injection where the 0° to 5° measurement was first recorded). The duration of assessment ended at the last available measurement or at the day of medical intervention for joints that did not recur and the recurrence day for recurrent joints.

b A recurrent joint was a joint evaluated by the investigator as having a worsening Dupuytren's contracture due to a palpable cord. The recurrence day was the visit where the recurrence was reported or the day of intervention if a joint was treated for a worsening Dupuytren's contracture. For joints reported as recurring in a previous study, the day of recurrence was the first visit with a fixed flexion contracture measurement of 20° or greater following the report of recurrence.

c The nominal rate of recurrence was the total number of recurrences occurring prior to the last day of the interval divided by the total number of joints (×100).

Retreatment of recurrent contractures
A study AUX-CC-862 was conducted in patients with Dupuytren's contracture who had recurrence of contracture in a joint that was effectively treated with Xiapex in a previous clinical study. No new safety signals were identified among subjects who were retreated with Xiapex. Most adverse events were non-serious, mild or moderate in intensity, and related to the local administration of Xiapex or to the finger extension procedure to facilitate cord disruption. The clinical efficacy in study AUX-CC-862 was similar to that reported in studies CORD I and CORD II. In study AUX-CC-862, 64.5% of recurrent MP joints and 45.0% of recurrent PIP joints achieved clinical success after retreatment with up to three injections of Xiapex.

In the retreatment study AUX-CC-862, 150 anti-AUX-I antibody positive samples and 149 anti-AUX-II antibody positive samples were assessed for potential cross-reactivity with human MMPs-1, -2, -3, -8, and -13. Results showed no cross-reactivity with any of the five MMPs tested.

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with Xiapex in all subsets of the paediatric population in the treatment of Dupuytren's contracture (see section 4.2 for information on paediatric use).

Peyronie's disease
The efficacy of Xiapex was evaluated in two randomized, double-blind, placebo-controlled studies, Study 1 (AUX-CC-803) and Study 2 (AUX-CC-804), in adult males with Peyronie's disease. The double–blind study population comprised 832 male patients of whom 551 patients received Xiapex

and 281 received placebo. The median age was 58 years (range 23 to 84 years). At study entry, patients must have had penile curvature deformity of at least 30 degrees in the stable phase of Peyronie's disease. Patients were excluded if they had a ventral curvature deformity, an isolated hourglass deformity or a calcified plaque that could have interfered with the injection technique. At baseline, penile pain was either not present or was mild in most (98%) patients.

In these studies, patients were given up to 4 treatment cycles of Xiapex or placebo (weeks 0, 6, 12, 18), and were followed in a non-treatment follow-up period (weeks 24-52). In each treatment cycle, two injections of Xiapex 0.58 mg or two injections of placebo were administered 1 to 3 days apart. A penile modelling procedure was performed on patients at the study site 1 to 3 days after the second injection of the cycle. The treatment cycle was repeated at approximately six-week intervals for up to three additional times, for a maximum of 8 total injection procedures and 4 total modelling procedures. In addition, patients were instructed to perform penile modelling at home for six weeks after each treatment cycle.
In Studies 1 and 2, the co-primary endpoints were:

- the percent change from baseline to Week 52 in penile curvature deformity **and**
- the change from baseline to Week 52 in the Bother domain of the Peyronie's Disease Questionnaire (PDQ)

The Bother domain score is a composite of the following patient-reported items: concern about erection pain, erection appearance, and the impact of Peyronie's disease on intercourse and on frequency of intercourse.

Xiapex treatment significantly improved penile curvature deformity in patients with Peyronie's disease compared with placebo (Table 9). The improvement in curvature deformity was numerically similar among patients with baseline deformity from 30 to 60 degrees and those with curvature deformity from 61 to 90 degrees.

Xiapex significantly reduced patient-reported bother associated with Peyronie's disease compared with placebo (Table 10). The reduction in the Bother domain score was numerically similar between patient groups stratified by degree of baseline curvature deformity (30 to 60 degrees and 61 to 90 degrees).

Table 8 provides the baseline disease characteristics for the study population and Tables 9 -10 provide the results of the co-primary efficacy endpoints measured in the 2 double-blind placebo-controlled studies AUX-CC-803 and AUX-CC-804.

Table 8. Baseline disease characteristics of patients[a] with Peyronie's Disease (PD)

	Study 1		Study 2	
	XIAPEX N=277	**Placebo** N=140	**XIAPEX** N=274	**Placebo** N=141
Mean age (years) (Min-Max)	57.9 (28 - 79)	58.2 (30 - 81)	57.3 (23 - 84)	57.6 (33 - 78)
Mean duration of PD (years) (Min-Max)	3.9 (1.0 - 35.9)	4.8 (1.0 - 50.8)	4.2 (1.1 - 30.9)	3.4 (1.1 - 17.1)
Mean Penile Curvature Deformity **(**degrees) (Min-Max)	48.8 (30-90)	49.0 (30-89)	51.3 (30-90)	49.6 (30-85)
Peyronie's Disease Questionnaire (PDQ)[b], – Mean Patient-Reported PD Bother Domain Score (range: 0-16) [c]	7.5	7.4	7.4	8.2
History of Erectile Dysfunction N (%)	128 (46.2)	75 (53.6)	134 (48.9)	76 (53.9)

a Subjects were from ITT population and received at least one dose of study drug in Study 1 or 2

b Each PDQ assessment required subjects to have had vaginal intercourse in the 3 months prior to completion

c Higher scores represent worse symptoms

Table 9. Mean percent change in penile curvature deformity from baseline to week 52 – Studies 1 and 2

	Study 1		Study 2	
	XIAPEX N=199	**Placebo N=104**	**XIAPEX N=202**	**Placebo N=107**
Baseline Mean (degrees)	48.8°	49.0°	51.3°	49.6°
Mean Percent Change [a]	-35.0%	-17.8%	-33.2%	-21.8%
Treatment Difference (95% CI)	-17.2% [b] (-26.7%, -7.6%)		-11.4% [b] (-19.5%, -3.3%)	

a Mean percent change, treatment difference, 95% CI, and p-value were based on an ANOVA model with factors for treatment, stratum of baseline penile curvature, and their interaction and using last observation carried forward (LOCF) in the modified intent-to-treat (mITT) population. The mITT population was defined as all randomized subjects who had both a penile curvature deformity measurement and a PDQ assessment at baseline and at one or more subsequent time points.

b p-value < 0.01

Table 10. Mean Change in Peyronie's Disease Bother Domain Score from Baseline to Week 52 - Studies 1 and 2

	Study 1		Study 2	
	XIAPEX N=199	**Placebo N=104**	**XIAPEX N=202**	**Placebo N=107**
Baseline Mean	7.5	7.4	7.4	8.2
Mean Change [a]	-2.8	-1.6	-2.6	-1.5
Treatment Difference (95% CI)	-1.2 [b] (-2.4, -0.03)		-1.1 [b] (-2.1, -0.002)	

a Mean change, treatment difference, 95% CI, and p-value all based on an ANOVA model with factors for treatment, stratum of baseline penile curvature, and their interaction and using last observation carried forward (LOCF) in the modified intent-to-treat (mITT) population. The mITT population was defined as all randomized subjects who had both a penile curvature deformity measurement and a PDQ assessment at baseline and at one or more subsequent time points.

b p-value < 0.05.

Xiapex was not associated with shortening of penile length in clinical trials in the treatment of Peyronie's disease.

An open label phase 3 study, AUX-CC-806, evaluated the safety and efficacy of Xiapex. The study inclusion and exclusion criteria as well as the treatment schedule and the co-primary efficacy endpoints were the same as in the pivotal AUX-CC-803 and AUX-CC-804 studies. Patients were however followed up to 36 weeks. A total of 189 patients were enrolled and treated with Xiapex. All patients had participated in and completed the studies AUX-CC-803 or AUX-CC-804, in which they had received placebo.

The median age of the patients included was 60, ranging between 33 and 77 years. The median duration of disease was 4.9 years (range 2.0 to 27.9 years). Erectile dysfunction was reported in 52.9% of patients, and 27.5% reported previous trauma to penis.

Tables 11-12 provide the results of the co-primary efficacy endpoints measured in the open label phase 3 study AUX-CC-806.

Table 11. Mean Percent Change from Baseline in Curvature Deformity at Week 36 (LOCF) (mITT* Population) – study AUX-CC-806

	Xiapex N=126
Baseline value	
Mean (SD)	46.9 (12.00)
Min, Max	30, 85
Week 36 value (LOCF)	
Mean (SD)	29.9 (15.56)
Min, Max	0, 80
% change from baseline	
Mean (SD)	-36.3 (30.72)
Min, Max	-100, 100
95% CI of mean**	-41.6, -30.9

*The mITT population was defined as all randomized subjects who had both a penile curvature deformity measurement and a PDQ assessment at baseline and at one or more subsequent time points.

**Based on the 95% CI of the mean not including zero, the percent change from baseline was considered statistically significant.

Table 12. Mean Change from Baseline in Peyronie's Disease Bother Score at Week 36 (LOCF) (mITT* Population) – study AUX-CC-806

	Xiapex N=126
Baseline value	
Mean (SD)	6.3 (3.60)
Min, Max	1, 15
Week 36 value (LOCF)	
Mean (SD)	3.9 (3.65)
Min, Max	0, 16
Change from baseline	
Mean (SD)	-2.4 (3.34)
Min, Max	-12, 7
95% CI of mean**	-3.0, -1.8

*The mITT population was defined as all randomized subjects who had both a penile curvature deformity measurement and a PDQ assessment at baseline and at one or more subsequent time points.

**Based on the 95% CI of the mean not including zero, the mean change from baseline was considered statistically significant.

As an exploratory analysis, female sexual partners completed two questionnaires at both the screening visit and week 36: the PDQ for Female Sexual Partners (an adaptation of Peyronie's disease bother and psychological symptom domains of the PDQ for men, scoring from 0-12) and the Female Sexual Function Index (FSFI, scale from 2-36, where a higher score represents better sexual functioning). Altogether 30 female partners participated in the study. At baseline, the mean (SD) Female PDQ score was 4.7 (3.61) and 2.7 (3.06) at week 36, i.e. a change from baseline of -2.0. The mean (SD) FSFI score was 20.56 (10.08) at baseline and 26.72 (7.73) at week 36, a change from baseline of 7.54.

Long-term efficacy and safety

A phase 4, non-treatment, long-term follow-up study (AUX-CC-810) was undertaken to evaluate the efficacy and safety up to 5 years after the first injection of Xiapex in the pivotal 12-month double-blind placebo-controlled phase 3 studies or in the 9-month open-label phase 3 studies. Through the 5 year follow up period (Table 13), subjects demonstrated an improvement in penile curvature and in PDQ bother compared with the last observed value from the previous phase 3 studies. There were no changes in the international index of erectile function (IIEF) scores. No new safety signals were identified during the 5 year follow-up period.

Table 13: Long Term Efficacy variables – study AUX-CC-810

	Baseline[a]	**Reference[b]**	**Year 2**	**Year 3**	**Year 4**	**Year 5**
Curvature* (degrees)	N=247	N=247	N=51	N=43	N=225	N=180
Mean±SD	51.8±15.04	31.0±16.10	25.8±12.99	25.2±13.31	29.1±17.21	27.0±16.13
Median	50.0	30.0	26.0	27.0	30.0	29.5
Min, Max	30, 90	0, 81	0, 55	0, 60	0, 85	0, 70
PDQ bother**	N=183	N=183	N=34	N=29	N=154	N=123
Mean±SD	6.5±3.47	3.4±3.30	3.2±3.30	2.7±2.84	2.5±3.01	2.4±2.89
Median	6.0	2.0	2.5	1.0	1.0	1.0
Min, Max	0, 15	0, 14	0, 14	0, 9	0, 12	0, 13

	Baseline[a]	Reference[b]	Year 2	Year 3	Year 4	Year 5
IIEF erectile function**	N=181	N=183	N=37	N=31	N=167	N=134
Mean±SD	23.2±6.47	24.9±6.12	22.9±7.70	22.9±8.13	23.3±7.54	23.6±7.48
Median	26.0	27.0	26.0	26.0	27.0	27.0
Min, Max	2, 30	3, 30	3, 30	1, 30	3, 30	1, 30

[a] Baseline was defined as the last observation prior to the first injection of Xiapex in the previous phase 3 study (i.e AUX-CC-802, AUX-CC-803, AUX-CC-804 or AUX-CC-806)
[b] Reference was defined as the last post-baseline non-missing observed value from the previous phase 3 study (i.e AUX-CC-802, AUX-CC-803, AUX-CC-804 or AUX-CC-806)
* Note: 29 subjects were excluded from this analysis. 9 subjects received commercial Xiapex and 2 subjects had penile implant during the course of the non-treatment study (AUX-CC-810), and 18 subjects had prior surgical intervention for the treatment of Peyronie´s Disease.
**Note: 22 subjects were excluded from this analysis. 9 subjects received commercial Xiapex and 1 subject had penile implant during the course of the non-treatment study (AUX-CC-810), and 12 subjects had prior surgical intervention for the treatment of Peyronie´s Disease.

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with Xiapex in all subsets of the paediatric population in the treatment of Peyronie's disease (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption
Following administration of either a single dose of 0.58 mg of Xiapex to 16 patients with Dupuytren's contracture, or two concurrent injections of 0.58 mg of Xiapex in the same hand in 12 patients with Dupuytren's contracture, no quantifiable levels of Xiapex were detected in plasma from 5 minutes to 30 days post injection.

Following each of two intralesional administrations, separated by 24 hours, of Xiapex 0.58 mg into the penile plaque of 19 patients with Peyronie's disease, plasma levels of AUX-I and AUX-II in patients with quantifiable levels (82% and 40% for AUX-I and AUX-II, respectively) were minimal and short-lived. The maximal individual plasma concentrations of AUX-I and AUX-II were <29 ng/mL and <71 ng/mL, respectively. All plasma levels were below the limits of quantification within 30 minutes following dosing. There was no evidence of accumulation following two sequential injections of Xiapex administered 24 hours apart. No patients had quantifiable plasma levels 15 minutes after modelling of plaque on Day 3 (i.e., 24 hours after Injection 2 on Day 2).

Distribution
There has been no evidence of systemic toxicity to date in the clinical studies conducted with Xiapex administered through localized injection into the Dupuytren's cord or into the Peyronie's plaque.

Biotransformation
Because Xiapex is not a substrate for cytochrome P450 or other medicinal product metabolizing enzyme pathways, and because no active metabolites are expected, no metabolism studies have been performed.

Elimination
No formal studies on elimination have been performed. There is no quantifiable systemic exposure following a single injection of Xiapex in patients with Dupuytren's contracture and only minimal and short-lived systemic exposure in patients with Peyronie's disease.

Special population
No dose adjustment is necessary in any special patient groups e.g., Elderly, Renally or Hepatically Impaired, by Gender or Race.

Paediatric population
Xiapex has not been studied in children and adolescents aged 0-18 years and hence no pharmacokinetic data are available.

5.3 Preclinical safety data

Repeated dose toxicity
In a single-dose phase or 61-day repeat-dose phase (3 times a week every 3 weeks for 3 cycles) study of intrapenile administration of collagenase *clostridium histolyticum* in dogs at exposures lower than or equal to the maximum recommended human dose on a mg/m^2 basis, there was no evidence of systemic toxicity.

Reproductive toxicity
When Xiapex was given intravenously every other day to male and female rats before cohabitation and through mating and implantation, no effects on the oestrus cycle, tubal transport, implantation and pre-implantation development and/or on libido or epididymal sperm maturation were noted with intravenous doses up to 0.13 mg/dose (approximately 11 times the human dose on a mg/m^2 basis). There were no adverse reactions on early embryonic development (indicating no evidence of teratogenicity) in rats. No systemic toxicity was observed in this study at any dose level.

Mutagenicity
Collagenase *clostridium histolyticum* was not mutagenic in *Salmonella typhimurium* (AMES test) and was not clastogenic in both an *in vivo* mouse micronucleus assay and an *in vitro* chromosomal aberration assay in human lymphocytes.

Carcinogenicity
Standard two-year rodent bioassays have not been performed with Xiapex. Thus, the carcinogenic risk is unknown.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder
Sucrose
Trometamol
Hydrochloric acid 2.4% w/w (for pH adjustment)

Solvent
Calcium chloride dihydrate
Sodium chloride
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

3 years.

After reconstitution, immediate use is recommended. Reconstituted Xiapex can be kept at ambient room temperature (20ºC-25ºC) for up to one hour or refrigerated 2ºC-8˚C for up to 4 hours prior to administration. If refrigerated, the reconstituted solution must be allowed to return to ambient room temperature (20ºC-25ºC) for approximately 15 minutes before use.

6.4 Special precautions for storage

Store in a refrigerator (2ºC-8ºC).
Do not freeze.

For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Xiapex powder is supplied in a clear glass vial (3 ml, type I glass) with rubber stopper, aluminium seal and flip-off cap (polypropylene).

Solvent: 3 ml solution supplied in a clear glass vial (5 ml, type I glass) with rubber stopper, aluminium seal and flip-off cap (polypropylene).

Pack of 1 vial of powder and 1 vial of solvent

6.6 Special precautions for disposal and other handling

Instructions for use and handling

Preparation - Reconstitution procedure

The vial containing Xiapex and the vial containing the solvent for solution for injection for reconstitution must be refrigerated. Prior to use, the vial containing Xiapex and the vial containing the solvent for solution for reconstitution must be removed from the refrigerator and allowed to stand at room temperature for at least 15 minutes and no longer than 60 minutes. Each vial of Xiapex and sterile solvent for reconstitution should only be used for a single injection. If two cords of affected joints on the same hand are to be treated during a treatment visit, separate vials and syringes should be used for each reconstitution and injection.

Using an aseptic technique, the following procedure for reconstitution must be followed:

1. Dupuytren's contracture: The joint to be treated (MP or PIP) should be confirmed as the volume of solvent required for reconstitution is determined by the type of joint (PIP joint requires a smaller volume for injection).
   Peyronie's disease: The treatment area should be identified and marked with a surgical marker on the erected penis.

2. The flip-off plastic caps should be removed from both vials. The rubber stopper and surrounding surface of the vial containing Xiapex and the vial containing the solvent for reconstitution should be swabbed with sterile alcohol (no other antiseptics must be used).

3. Only the supplied solvent must be used for reconstitution; it contains calcium which is required for the activity of Xiapex. Using a sterile syringe calibrated with 0.01 ml graduations, the appropriate amount of solvent supplied should be withdrawn in order to deliver as follows:

Table 14. Volumes needed for administration

Treatment area	Solvent required for reconstitution	Injection volume to deliver Xiapex 0.58 mg dose†
Dupuytren's MP joints	0.39 ml	0.25 ml
Dupuytren's PIP joints	0.31 ml	0.20 ml
Peyronie's plaque	0.39 ml	0.25 ml

†Note that injection volume for delivery of a 0.58 mg dose is less than the total volume of solvent used for reconstitution.

4. The solvent should slowly be injected into the sides of the vial containing the lyophilised powder of Xiapex. The vial containing the solution should not be inverted or shaken. The solution should slowly be swirled to ensure that all of the lyophilised powder has gone into solution. The syringe and needle used for reconstitution are thereafter removed and discarded.

5. The solution should visually be inspected for particulate matter and discoloration prior to administration. The reconstituted solution of Xiapex must be clear. If the solution contains particles, is cloudy or discoloured, it should not be injected.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Swedish Orphan Biovitrum AB (publ)
SE-112 76 Stockholm
Sweden

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/671/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 28 February 2011
Date of latest renewal: 18 January 2016

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

ANNEX II

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

Auxilium Pharmaceuticals, LLC
102 Witmer Road, Horsham, PA 19044.
USA

Lonza AG
Lonzastrasse
3930 Visp
Switzerland

Name and address of the manufacturer responsible for batch release

Swedish Orphan Biovitrum AB (publ)
SE-112 76 Stockholm
Sweden

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

The MAH shall ensure that all physicians who are expected to prescribe/use Xiapex are appropriately trained in the correct administration of the medicinal product and experienced in the diagnosis and management of Dupuytren's contracture and Peyronie's disease.

The MAH, in agreement with the competent authorities in the Member States, shall implement, prior to the launch, an educational programme for physicians aiming to ensure proper injection placement to minimize occurrence of injection-related adverse events and to inform on expected and potential risks associated with the treatment.

The physician educational programme should contain the following key elements:

- Injection technique and dosing interval.
- Proper amount of volumes for both reconstitution and injection differences in the metocarpophalangeal (MP) and proximal interphalangeal (PIP) joints for Dupuytren's contracture and for the Peyronie's disease plaque.
- Recognition and treatment of severe immune-mediated reaction, including anaphylaxis.
- Information on bleeding risk in patients with coagulation disorders including those on concurrent anti-coagulation therapy.
- Information on the potential risk of matrix metalloproteinases (MMP) cross reactivity including the development of musculoskeletal syndrome and exacerbation/initiation of autoimmune disorders.
- Reminder of the need to report adverse events, including medication errors.
- The need to inform the patient about the signs and symptoms associated with the treatment and when to seek attention from the health care provider.
- The summary of product characteristics and the patient information leaflet.

- **Obligation to conduct post-authorisation measures**

Not applicable

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton containing 1 vial of powder and 1 vial of solvent

1. NAME OF THE MEDICINAL PRODUCT

Xiapex 0.9 mg powder and solvent for solution for injection
collagenase *clostridium histolyticum*

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each powder vial contains 0.9 mg collagenase *clostridium histolyticum*

3. LIST OF EXCIPIENTS

Powder: Contains sucrose, trometamol, hydrochloric acid
Solvent: Contains calcium chloride dihydrate, sodium chloride, water for injection

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection
1 vial of powder
1 vial of solvent

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intralesional use only

Reconstitute with appropriate volume before use.
Read the package leaflet before use.
For single use only

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE sight and REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Swedish Orphan Biovitrum AB (publ)
SE-112 76 Stockholm
Sweden

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/671/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC: {number}
SN: {number}
NN: {number}

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Xiapex powder vial label

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Xiapex 0.9 mg powder for injection
collagenase *clostridium histolyticum*
Intralesional use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Solvent vial for use with Xiapex label

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Solvent for Xiapex

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

3 ml

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Xiapex 0.9 mg powder and solvent for solution for injection
collagenase *clostridium histolyticum*

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Xiapex is and what it is used for

Xiapex is used for the treatment of two different conditions: **Dupuytren's contracture in adult patients with a palpable cord** and **Peyronie's disease in adult men**.

Dupuytren's contracture
This is a disease that causes your finger(s) to bend inward. This bending is called a contracture and is caused by the abnormal formation of a cord containing collagen under your skin. For many people, a contracture causes significant difficulties with performing everyday tasks like driving, shaking hands, playing sports, opening jars, typing or holding objects.

Peyronie's disease
This is a condition where adult men have a 'plaque' that can be felt and a curve to their penis. The disease can cause a change in the shape of the erect penis due to the abnormal build-up of scar tissue, known as a plaque, within the stretchy fibres of the penis. The plaque may interfere with the ability to get a straight erection because the plaque will not stretch as much as the rest of the penis. Men with Peyronie's disease may have an erection that is curved or bent.

The active substance in Xiapex is collagenase *clostridium histolyticum*, and this collagenase is produced using the microorganism *Clostridium histolyticum*. Xiapex is injected by your doctor into the cord in your finger/hand or plaque in your penis and works by breaking down the collagen in the cord or plaque.
For Dupuytren's disease, Xiapex breaks down the collagen forming the cord and thereby releasing the contracture completely or partly and enabling your finger(s) to be straighter.
For Peyronie's disease, Xiapex breaks down the collagen in the plaque that is causing your erect penis to curve, which may help the previously bent erection to become straighter and enable you to feel less bothered by your disease. The reduction of the curve achieved will vary between individuals.

2. What you need to know before you are given Xiapex

You must not be given Xiapex:
- If you are allergic to collagenase *clostridium histolyticum* or any of the other ingredients of this medicine (listed in section 6).
- For Peyronie's disease if the treatment of your plaque involves the tube (called the urethra) that your urine passes through.

Warnings and precautions
Talk to your doctor or pharmacist before you are given Xiapex.

Allergic reactions
Severe allergic reactions can happen in patients who receive Xiapex, because it contains proteins foreign to the human body.

Call your doctor right away if you have any of these symptoms of an allergic reaction after an injection of Xiapex:
- hives
- swollen face
- breathing trouble
- chest pain

The potential for a serious allergic reaction or the development of a musculoskeletal syndrome upon repeated use of Xiapex cannot be excluded. The symptoms of musculoskeletal syndrome could be joint or muscle pain, shoulder stiffness, hand swelling, fibrosis of the palms, and thickening or nodule forming of tendons. If you notice such symptoms you should inform your doctor.

Before you are given this medicine, make sure your doctor knows:
- if you have had an allergic reaction to a previous Xiapex injection.
- if you have a history of problems with the normal clotting of your blood or if you are taking any medicines to help control the normal clotting of your blood (known as anticoagulation medicines).
- if you are currently taking any anticoagulation medicines, you must not receive Xiapex within 7 days of last dose of your anticoagulation medicine. One exception is the use of up to 150 mg daily dose of acetylsalicylic acid (a substance present in many medicines used to prevent blood clotting) which can be taken.

If you are treated for Dupuytren's contracture

This medicine must only be injected into the collagen cord in your hand by your doctor. Your doctor will take care to avoid injecting into tendons, nerves or blood vessels. Incorrect injection into tendons, nerves or blood vessels may result in bleeding or damage and possible permanent injury to these structures. If your cord to be treated is attached to the skin, you are at higher risk of the skin splitting or tearing during the finger extension procedure following the injection of Xiapex.

Severe injury like e.g. finger necrosis or fracture could result in loss of finger or finger parts. Before finger manipulation procedure will be performed tell your doctor, if you have a condition affecting your bones, e.g. osteopenia or osteoporosis. Contact your doctor right away if you are concerned by increasing pain or symptoms in the fingers after the treatment.

Tell your doctor if you have previously received or are thinking about receiving Xiapex to treat a condition known as Peyronie's disease. This condition affects adult men, who have a 'plaque' that can be felt and a curve to their erect penis.

If you are treated for Peyronie's disease

This medicine must only be injected into the plaque in your penis by your doctor.

Penile fracture (corporal rupture) or other serious injury to the penis
Receiving an injection of Xiapex may cause damage to the tubes in your penis called the corpora. After treatment with Xiapex, one of these tubes may break during an erection. This is called a corporal rupture or penile fracture.
After treatment with Xiapex, blood vessels in your penis may also break, causing blood to collect under the skin (which is called a haematoma).

Symptoms of penile fracture (corporal rupture) or other serious injury to your penis may include:
- a popping sound or sensation in an erect penis
- sudden loss of the ability to maintain an erection
- pain in your penis
- purple bruising and swelling of your penis
- difficulty urinating or blood in the urine

Call your doctor right away if you experience any of the symptoms of penile fracture or serious injury to your penis listed above, as this may require surgical intervention.
Do not have sex or have any other sexual activity for at least 4 weeks after the second injection of a treatment cycle with Xiapex and after any pain and swelling has ceased and be cautious when resuming sexual activity.

Tell your doctor if you are thinking about receiving or have previously received Xiapex to treat a condition known as Dupuytren's contracture. In this condition, a cord forms in the tissue in the palm of the hand and causes one or more fingers to bend toward the palm so that they cannot be straightened.

Children and adolescents
There is no relevant use of Xiapex in children and adolescents aged 0-18 years for the treatment of Dupuytren's contracture or Peyronie's disease.

Other medicines and Xiapex
Tell your doctor if you are taking, have recently taken or might take any other medicines. This includes medicines to help control the normal clotting of your blood (known as anticoagulation medicines), anthraquinone derivatives, some antibiotics (tetracyclines and anthracyclines/anthraquinolones) used to treat infections. There are no known interactions with concomitant use of medicines for erectile dysfunction and Xiapex treatment.

Pregnancy and breast-feeding
Dupuytren's contracture
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before you are given this medicine.
There is no experience in the use of Xiapex in pregnant women therefore the use of Xiapex is not recommended in pregnancy, and treatment should be postponed until after pregnancy.

There is no experience in the use of Xiapex in breast-feeding women therefore the use of Xiapex is not recommended during breast-feeding.

Peyronie's disease
This condition does not occur in females.

Driving and using machines
If you experience dizziness, numbness or altered sensation, and headache immediately after an injection of Xiapex you must avoid potentially hazardous tasks such as driving or using machines until these effects have passed or until advised by your doctor.

Swelling and pain may impair the use of the treated hand in Dupuytren's disease.

Xiapex contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

3. How Xiapex is used

Only doctors that have been appropriately trained in the correct use of Xiapex and are experienced in the management of Dupuytren's or Peyronie's disease are allowed to give you treatment.

You will be given Xiapex as an injection directly into the area that is causing your finger/penis to bend (intralesional injection). Your doctor will perform all injections of Xiapex.

The recommended dose of your prescribed medicine is 0.58 mg.

Dupuytren's contracture
The total volume of the injection depends on the joint being treated. Your doctor will carefully select an area where the collagen cord is best accessible and will proceed with the injection into the cord.

After the injection, your doctor will place a dressing on your hand. You must limit motion of the treated finger for a day and it is not uncommon for the finger to straighten on its own for some patients. Until advised by your doctor, do not flex or extend the fingers of the injected hand. Do not attempt to disrupt the injected cord by self manipulation at any time. Elevate the injected hand as much as possible until the day after the finger extension procedure.

Your doctor will ask you to return approximately 24-72 hours after your injection to attempt to extend your finger to straighten it. Following extension of your finger, your doctor will fit you with a splint to wear at bedtime for up to 4 months.
If your finger is still not able to straighten during a follow-up visit with your doctor, you may need additional treatments with Xiapex which may be administered approximately 4 weeks after the first treatment. Injections and finger extension procedures may be administered up to 3 times per cord at approximately 4-week intervals. Injections in up to two cords or two affected joints in the same hand can be administered during a treatment visit. If the disease has resulted in multiple contractures, additional cords may be treated at other treatment visits approximately 4 weeks apart, as determined by your doctor.

Be sure to ask your doctor when you can resume normal activities after treatment with Xiapex. It is recommended to avoid strenuous activities of your finger until instructed further by your doctor. Your doctor may recommend you perform a series of finger flexion and extension exercises several times a day for several months.
Clinical study experience with Xiapex is currently limited to up to 3 injections per cord and up to a total of 8 injections in the hands.

Peyronie's disease
Your doctor will inject Xiapex into the plaque that is causing your penis to curve.

- Xiapex is given as part of a treatment cycle. In each treatment cycle, you will receive one injection of Xiapex, followed by a second injection on a separate day (1 to 3 days later).
- After each injection of Xiapex, your penis may be wrapped with a bandage. Your doctor will tell you when to remove the dressing.
- One to three days after the second injection of Xiapex in a treatment cycle, you will need to return to your doctor for a manual procedure that will help stretch and help straighten your penis. Your doctor will tell you when to come back for this.
- Your doctor will show you how to gently stretch and straighten your penis the right way. For further information see **"Instructions on how to gently stretch your penis"** and **"Instructions on how to gently straighten your penis" at the end of the Patient leaflet.**
- **You should only gently *stretch* your penis when you *do not have* an erection.** You should gently stretch your penis 3 times a day for 6 weeks after each treatment cycle.
- **You should only gently *straighten* your penis if you *have* an erection that happens without any sexual activity (spontaneous erection).** You should gently straighten your penis 1 time a day for 6 weeks after each treatment cycle.
- Your doctor will tell you when you can resume sexual activity after each treatment cycle.

- Your doctor will also tell you when to come back if more treatment cycles are needed.

Clinical study experience with Xiapex is currently limited to four treatment cycles in which a total of 8 injections may be administered into the plaque causing the curvature.

Tell your doctor right away if you have trouble stretching or straightening your penis, or if you have pain or other concerns.

If you receive more Xiapex than you should
As this medicine is administered to you by your doctor it is very unlikely that you will be given an incorrect dose. In the unlikely event that your doctor administers a higher dose than recommended, you may experience an increase in the severity of possible side effects listed in section 4 "Possible Side Effects".

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Allergic reaction
Severe allergic reaction has been reported uncommonly (1 case). Please consult a doctor immediately if you experience any signs or symptoms of a serious allergic reaction, e.g., wide spread redness or rash, swelling, tightness in the throat or difficulty breathing. **You must not be given Xiapex** if you know that you have had a serious allergic reaction to collagenase or any of the other ingredients.

Dupuytren's contracture

Most of the side effects that occurred in the clinical studies were mild or moderate in severity and were localised to the hand treated.

The following side effects have been seen with Xiapex administered in up to two cords or joints per treatment visit:

Very common side effects (may affect more than 1 in 10 people):
- reactions at the injection site like bleeding, pain, swelling, tenderness and bruising
- itching in the hand
- feeling of pain in the hand, wrist or arm
- swollen or enlarged glands near the elbow or under the arm
- swelling in the hand or arm

Common side effects (may affect up to 1 in 10 people):
- reactions at the injection site like pain, warmth, swelling, presence of a blister, redness of skin and/or skin rash
- skin wound at the site of injection
- skin wound, blood blister
- painful glands near the elbows or under the arm
- joint swelling and pain
- burning sensation, partial loss of sensitivity, feeling of "pins and needles" or numbness
- dizziness, headache, nausea
- increased perspiration

Uncommon side effects (may affect up to 1 in 100 people):
- rupture of a tendon, ligament injury
- low blood platelet count
- swelling of the eyelid
- allergic reaction
- chronic pain
- discomfort, injury, paralysis of the limb
- tremor/shaking, increased sensitivity to stimuli
- fainting
- vomiting, diarrhoea, upper abdominal pain
- rash, eczema
- stiffness, creaking of the joints
- muscle spasm, muscle weakness, musculoskeletal stiffness or discomfort
- feeling of pain in the groin, shoulder, chest wall, or neck
- swelling
- fever, general pain, discomfort, tiredness, feeling hot, malaise, flu-like illness
- cold intolerance of the treated fingers
- reactions at the site of injection including peeling of the skin, skin discoloration, infection, pain, skin tightness, numbness, irritation or nodules, scab, wound
- increased liver enzymes
- agitation, disorientation, irritability, restlessness, difficulty sleeping
- shortness of breath, hyperventilation
- inflammation of the lymph nodes (lymphadenitis), inflammation of lymphatic channels (lymphangitis) leading to reddened skin with elevated borders, tender and warm, usually accompanied by a red streak, enlarged lymph nodes

Frequency of side effects not known
- fractured finger
- loss of finger or finger parts

Peyronie's disease

Penile Fracture (corporal rupture) or other serious injury to the penis
Penile Fracture (corporal rupture) or other serious injury to the penis has uncommonly occurred. **Call your doctor right away if you experience any of the symptoms of penile fracture or other serious injury to your penis which are as follows:** a popping sound or sensation in an erect penis, sudden loss of the ability to maintain an erection, pain in your penis, purple bruising and swelling of your penis, difficulty urinating or blood in the urine, a collection of blood under the skin at the injection site.

Most of the side effects that occurred in the clinical studies were mild or moderate in severity and most resolved within 2 weeks of the injection.

The following side effects have been seen with Xiapex:

Very common side effects (may affect more than 1 in 10 people)**:**
- bruising or swelling of the penis and pain in the penis
- a small collection of blood under the skin at the injection site

Common side effects (may affect up to 1 in 10 people)**:**
- reactions at the injection site such as presence of a blister, swelling, itching or a solid raised area under the skin
- pain at the injection site and above the penis
- blister or redness/discolouration of the penis
- genital itchiness

- painful erection, painful sex and erectile dysfunction.

Uncommon side effects (may affect up to 1 in 100 people)**:**
- lymph node pain and swollen lymph nodes
- increased white blood cells
- fast heart rate
- ringing in the ear
- abdominal swelling
- constipation
- feeling hot
- injection site rash
- fever
- weakness
- chills
- flu-like illness
- drainage from a blister on the penis
- tenderness
- allergic reaction
- fungal skin infection
- infection
- upper respiratory infection
- skin cut
- open wound
- collection of blood outside of a blood vessel on scrotum
- joint injury
- popping sound/sensation indicating penile fracture
- blood sugar increased
- blood pressure increased
- water retention
- back pain
- groin pain and discomfort
- thickening near ligament at base of penis
- tenderness in ligament at base of penis
- headache
- dizziness
- unpleasant taste
- abnormal sensation
- burning sensation
- increased/decreased sensitivity to stimuli to senses
- abnormal dreams
- depression
- avoidance of sex
- painful/increased urination
- scar tissue in penis
- penis disorder
- worsening of Peyronie’s disease
- sexual dysfunction
- scrotal redness, swelling and pain
- genital discomfort and bruising
- pelvic pain
- penis size reduced
- formation of a blood clot inside the penile vein
- cough
- small area of inflammation

- night sweats
- sore on the skin of the penis
- skin rash producing redness
- skin disorder/irritation
- collection of blood outside the blood vessels
- bruising
- disease of the lymph vessels
- superficial vein inflammation

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Xiapex

Keep this medicine out of the sight and reach of children.

Your doctor must not use this medicine after the expiry date which is stated on the carton and vial label after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator at 2ºC-8ºC. Do not freeze.

After reconstitution, immediate use of the medicine is recommended. Reconstituted Xiapex can be kept at ambient room temperature (20ºC-25ºC) for up to one hour or refrigerated at 2ºC-8˚C for up to 4 hours prior to administration. If refrigerated, the reconstituted solution must be allowed to return to ambient room temperature (20ºC-25ºC) for approximately 15 minutes before use.

Your doctor must not use Xiapex if the reconstituted solution is discoloured or contains particles. The solution must be clear, colourless with no lumps or flakes or particles.

Your doctor will take care of storing, handling and disposing of Xiapex. Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Xiapex contains
- The active substance is collagenase *clostridium histolyticum*. Each vial of Xiapex contains 0.9 mg of collagenase *clostridium histolyticum*.
- The other ingredients are sucrose, trometamol and hydrochloric acid 2.4% w/w (for pH adjustment).
- The solvent contains calcium chloride dihydrate, sodium chloride and water for injections.

What Xiapex looks like and contents of the pack
Xiapex is a powder and solvent for solution for injection. The white lyophilized powder is supplied in a 3 ml type I clear glass vial with rubber stopper, aluminium seal and flip-off plastic cap.

The solvent that is used to dissolve the powder is a clear colourless liquid. 3 ml solution is supplied in a 5 ml type I clear glass vial with rubber stopper, aluminium seal and flip-off plastic cap.

Xiapex is supplied in a pack containing 1 vial of Xiapex powder and 1 vial of solvent.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder
Swedish Orphan Biovitrum AB (publ), SE-112 76 Stockholm, Sweden

Manufacturer
Swedish Orphan Biovitrum AB (publ), SE-112 76 Stockholm, Sweden

This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/.

The following information is intended for healthcare professionals only:

Instructions for use and handling

<u>Dupuytren's contracture</u>

1. Preparation - Reconstitution procedure

The single dose vial containing Xiapex and the single dose vial containing the solvent for solution for injection for reconstitution must be refrigerated.

1. Before use, remove the vial containing the lyophilized powder of Xiapex and the vial containing the diluent for reconstitution from the refrigerator and allow the two vials to stand at room temperature for at least 15 minutes and no longer than 60 minutes. Visually inspect the vial containing Xiapex. The cake of lyophilized powder should be intact and white in colour.

2. Confirm the joint to be treated (metacarpophalangeal [MP] or proximal interphalangeal [PIP]) as the volume of solvent required for reconstitution is determined by the type of joint (PIP joint requires a smaller volume for injection).

3. After removal of the flip-off cap from each vial, using aseptic technique swab the rubber stopper and surrounding surface of the vial containing Xiapex and the vial containing the diluent for reconstitution with sterile alcohol (no other antiseptics should be used).

4. Use only the supplied diluent for reconstitution. The diluent contains calcium which is required for the activity of Xiapex.

5. Using a 1 ml syringe with 0.01 ml graduations with a 27-gauge 12-13 mm needle (not supplied), withdraw the correct volume of the **diluent supplied**:

    - **<u>0.39 ml of solvent for cords affecting a MP joint in Dupuytren's contracture</u>**
    - **<u>0.31 ml of solvent for cords affecting a PIP joint in Dupuytren's contracture</u>**

6. Inject the diluent slowly into the sides of the vial containing the lyophilized powder of Xiapex. Do not invert the vial or shake the solution. Slowly swirl the solution to ensure that all of the lyophilized powder has gone into solution.

7. The reconstituted Xiapex solution can be kept at room temperature (20º to 25ºC) for up to one hour or refrigerated at 2º to 8°C for up to 4 hours prior to administration. If the reconstituted Xiapex solution is refrigerated, allow this solution to return to room temperature for approximately 15 minutes before use.

8. Discard the syringe and needle used for reconstitution and the diluent vial.

9. When administering two injections in the same hand during a treatment visit, use a new syringe and separate vial of reconstituted solution (containing 0.58 mg of Xiapex) for the second injection. Repeat steps 1 through 8.

2. Identification of treatment area

1. Prior to each treatment cycle, identify the treatment area as follows:
Confirm the joint to be treated (metacarpophalangeal [MP] or proximal interphalangeal [PIP]) as the volume of solvent required for reconstitution is determined by the type of joint (PIP joint requires a smaller volume for injection).

3. Injection procedure

Administration of a local anaesthetic medicinal product prior to injection of Xiapex is not recommended, as it may interfere with proper placement of the injection.

1. The reconstituted Xiapex solution should be clear. Inspect the solution visually for particulate matter and discolouration prior to administration. If the solution contains particulates, is cloudy, or is discoloured, do not inject the reconstituted solution.

2. Reconfirm the cord to be injected. The site chosen for injection must be the area where the contracting cord is maximally separated from the underlying flexor tendons and where the skin is not intimately adhered to the cord.

3. When administering two injections in the same hand during a treatment visit, begin with the affected finger in the most ulnar aspect of the hand and continue toward the radial aspect (eg, fifth finger to index finger). Within each finger, begin with the affected joint in the most proximal aspect of the finger and continue toward the distal aspect (eg, MP to PIP). For each injection, follow steps 4-10.

4. Apply antiseptic at the site of the injection and allow the skin to dry.

5. Using a new sterile, hubless syringe with 0.01 ml graduations and a permanently fixed, 26 or 27 gauge, 12 or 13 mm needle (not supplied), withdraw the adequate **volume of reconstituted solution** for a 0.58 mg dose of Xiapex required for injection to deliver:
   - **0.25 ml of reconstituted Xiapex for cords affecting a MP joint or**
   - **0.20 ml of reconstituted Xiapex for cords affecting a PIP joint.**

6. Use caution with cords as they approach the PIP flexion crease area. If injecting into a cord affecting the PIP joint of the fifth (little) finger, care must be taken to inject as close to the palmar digital crease as possible and not to insert more than 2 mm to 3 mm in depth. For PIP joints do not inject more than 4 mm distal to the palmar digital crease.

7. With your non-dominant hand, secure the patient's hand to be treated while simultaneously applying tension to the cord. With your dominant hand, place the needle into the cord, using caution to keep the needle within the cord. Avoid having the needle tip pass completely through the cord to help minimise the potential for injection of Xiapex into tissues other than the cord. After needle placement, if there is any concern that the needle is in the flexor tendon, apply a small amount of passive motion at the distal interphalangeal (DIP) joint. If insertion of the needle into a tendon is suspected or paresthesia is noted by the patient, withdraw the needle and reposition it into the cord. If the needle is in the proper location, there will be some resistance noted during the injection procedure. See Figure 1 below for an illustration of the injection technique.

8. After confirming that the needle is correctly placed in the cord, inject approximately one-third of the dose.

9. Next, keeping the needle under the skin at all times, withdraw the needle tip from the cord and reposition it in a slightly more distal location (approximately 2-3 mm) to the initial injection in the cord and inject another one-third of the dose.

10. Again keeping the needle under the skin at all times, withdraw the needle tip from the cord and reposition it a third time proximal to the initial injection (approximately 2-3 mm) and inject the final portion of the dose into the cord (see Figure 2).

The figures 1 and 2 below are for illustrative purposes only and may not be representative of the precise location of anatomical structures in an individual patient.

Figure 1: Illustration of the injection technique.

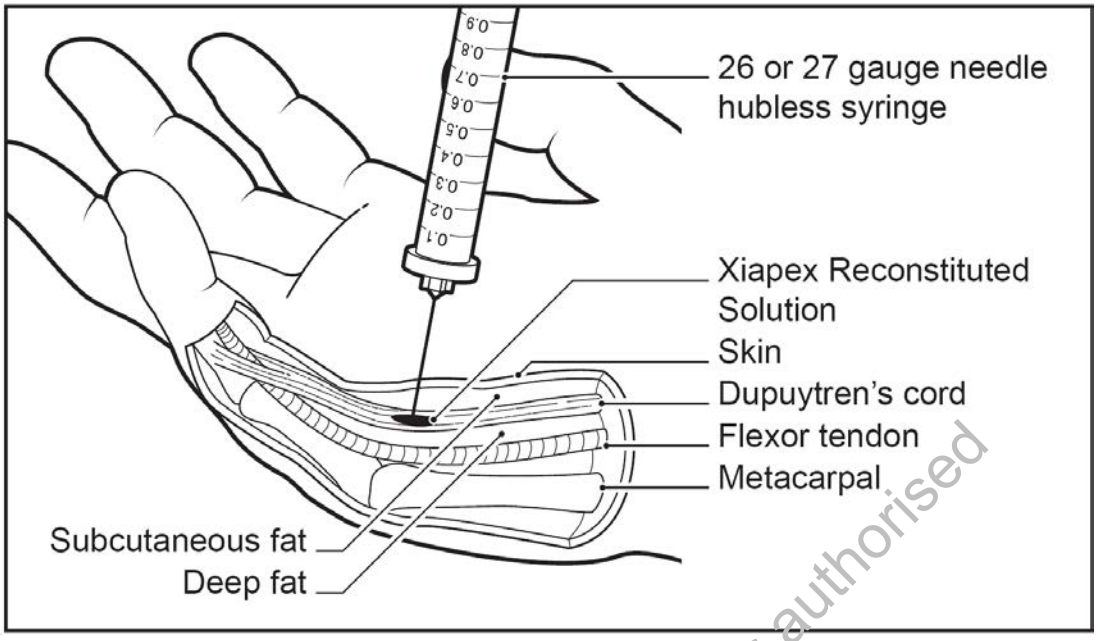
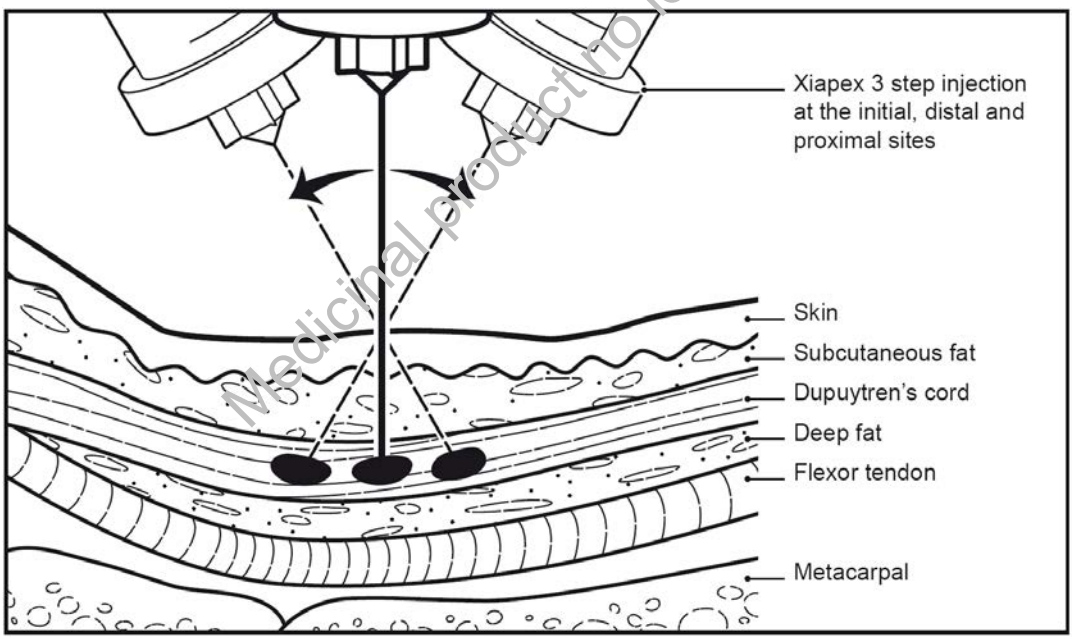


Figure 2: Three step injection of Xiapex into the cord.



11. Wrap the patient's treated hand with a soft, bulky, gauze dressing.

12. Discard the unused portion of the reconstituted solution and solvent after injection. Do not store, pool, or use any vials containing unused reconstituted solution or solvent.

13. Patients should be instructed:
    - Not to flex or extend the fingers of the injected hand to reduce extravasation of Xiapex out of the cord until the finger extension procedure is completed.
    - Not attempt to disrupt the injected cord by self manipulation at any time.

- To elevate the injected hand as much as possible until the day after the finger extension procedure.
- To promptly contact their doctor if there is evidence of infection (e.g., fever, chills, increasing redness or oedema) or trouble bending the finger after the swelling goes down (symptoms of tendon rupture).
- To return to see their physician approximately 24-72 hours after each injection for an examination of the injected hand and a possible finger extension procedure to disrupt the cord.

4. Finger extension procedure

1. At the follow-up visit approximately 24-72 hours after injection, determine if the contracture has resolved. If a cord contracture remains, a passive finger extension procedure will be performed in an attempt to disrupt the cord.

2. If cords of two affected joints in one finger were treated, perform the finger extension procedure on the cord affecting the MP joint before performing the procedure on the cord affecting the PIP joint.

3. Local anaesthesia may be used, if needed, during the finger extension procedure.

4. While the patient's wrist is in the flexed position, apply moderate stretching pressure to the injected cord by extending the finger for approximately 10 to 20 seconds. For cords affecting the PIP joint, perform the finger extension procedure when the MP joint is in the flexed position.

5. If the first finger extension procedure does not result in disruption of the cord, a second and third attempt can be performed at 5- to 10-minute intervals. No more than 3 attempts per affected joint are recommended to disrupt a cord.

6. If the cord has not disrupted after 3 attempts of extension per cord, a follow-up visit may be scheduled approximately 4 weeks after the injection. If, at that subsequent visit the contracted cord persists, an additional injection and finger extension procedure may be performed.

7. Following the finger extension procedure(s) and fitting patient with a splint (with treated joint in maximum extension), patients should be instructed to:
   - Not perform strenuous activity with the injected hand until advised to do so.
   - Wear the splint at bedtime for up to 4 months.
   - Perform a series of finger flexion and extension exercises several times a day for several months.

The following information is intended for Peyronie's disease patients only:

Instructions on how to gently stretch your penis

Gently stretch your penis 3 times a day. Only stretch your penis if your penis is not hard (erect).

- With one hand, hold the tip of your penis with your fingers. With the other hand, hold the base of your penis with the fingers (see Figure 3).
- Gently pull your penis away from your body to its full length and hold the stretch for 30 seconds.
- Let go of the tip of your penis and let your penis return to its normal length.

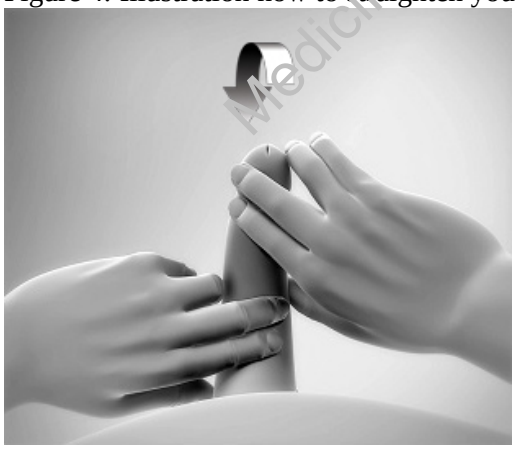
Figure 3: Illustration how to stretch your penis

Instructions on how to gently straighten your penis

Gently straighten your penis one time a day. Only straighten your penis if you have an erection that happens without any sexual activity (spontaneous erection). Bending your penis should not cause any pain or discomfort.

- With one hand hold your penis. With your other hand, gently bend your penis in the opposite direction of the curve (see Figure 4). Hold the penis in this more straightened position for 30 seconds, then let go.

Figure 4: Illustration how to straighten your penis



The following information is intended for healthcare professionals only:

Instructions for use and handling

<u>Peyronie's disease</u>

1. Preparation - Reconstitution procedure

The single dose vial containing Xiapex and the single dose vial containing the solvent for solution for injection for reconstitution must be refrigerated.

a) Before use, remove the vial containing the lyophilized powder of Xiapex and the vial containing the diluent for reconstitution from the refrigerator and allow the two vials to stand at room temperature for at least 15 minutes and no longer than 60 minutes. Visually inspect the vial containing Xiapex. The cake of lyophilized powder should be intact and white in colour.

b) After removal of the flip-off cap from each vial, using aseptic technique swab the rubber stopper and surrounding surface of the vial containing Xiapex and the vial containing the diluent for reconstitution with sterile alcohol (no other antiseptics should be used).

c) Use only the supplied diluent for reconstitution. The diluent contains calcium which is required for the activity of Xiapex.

d) Using a 1 ml syringe with 0.01 ml graduations with a 27 gauge 12-13 mm needle (not supplied), withdraw the correct volume of the **diluent supplied**:

- **<u>0.39 ml of solvent for the penile plaque in Peyronie's disease</u>**

e) Inject the diluent slowly into the sides of the vial containing the lyophilized powder of Xiapex. Do not invert the vial or shake the solution. Slowly swirl the solution to ensure that all of the lyophilized powder has gone into solution.

f) The reconstituted Xiapex solution can be kept at room temperature (20º to 25ºC) for up to one hour or refrigerated at 2º to 8°C for up to 4 hours prior to administration. If the reconstituted Xiapex solution is refrigerated, allow this solution to return to room temperature for approximately 15 minutes before use.

g) Discard the syringe and needle used for reconstitution and the diluent vial.

2. Identification of treatment area

a) Prior to each treatment cycle, identify the treatment area as follows:
- Induce a penile erection
- Locate the plaque at the point of maximum concavity (or focal point) in the bend of the penis
- Mark the point with a surgical marker. This indicates the target area in the plaque for Xiapex deposition

3. Injection procedure

a) The reconstituted Xiapex solution should be clear. Inspect the solution visually for particulate matter and discolouration prior to administration. If the solution contains particulates, is cloudy, or is discoloured, do not inject the reconstituted solution.

b) Apply antiseptic at the site of the injection and allow the skin to dry.

c) Administer suitable local anaesthetic, if desired.

d) Using a new hubless syringe containing 0.01 ml graduations with a permanently fixed 27-gauge 12 or 13 mm needle (not supplied), withdraw a volume of 0.25 ml of **reconstituted solution (containing 0.58 mg of Xiapex).**

e) The penis should be in a flaccid state before Xiapex is injected. Place the needle tip on the side of the target plaque in alignment with the point of maximal concavity. Orient the needle so that it enters the plaque from the side, NOT downwards or perpendicularly towards the corpora cavernosum.

f) Insert and advance the needle transversely through the width of the plaque, towards the opposite side of the plaque without passing completely through it. Proper needle position is tested and confirmed by carefully noting resistance to minimal depression of the syringe plunger.

g) With the tip of the needle placed within the plaque, initiate injection, maintaining steady pressure to slowly inject the drug into the plaque. Withdraw the needle slowly so as to deposit the full dose along the needle track within the plaque. For plaques that are only a few millimetres in width, the distance of withdrawal of the syringe may be very minimal. The goal is always to deposit the full dose entirely within the plaque.

h) Upon complete withdrawal of the needle, apply gentle pressure to the injection site. Apply a dressing as necessary.

i) Discard the unused portion of the reconstituted solution and diluent after each injection. Do not store, pool, or use any vials containing unused reconstituted solution or diluent.

j) The second injection of each treatment cycle should be made approximately 2 to 3 mm apart from the first injection.

4. Penile modelling procedure

Penile modelling helps relieve curvature deformity and straighten the penile shaft. At a follow-up visit 1 to 3 days after the second injection of each treatment cycle, perform a penile modelling procedure (as described below) on the flaccid penis to stretch and elongate the plaque that Xiapex has disrupted:

- Administer suitable local anaesthetic, if desired.
- Wearing gloves, grasp the plaque or indurated portion of the flaccid penis about 1 cm proximal and distal to the injection site. Avoid direct pressure on the injection site.
- Using the target plaque as a fulcrum point, use both hands to apply firm, steady pressure to elongate and stretch the plaque. The goal is to gradually create bending opposite to the patient's penile curvature, with stretching to the point of moderate resistance. Hold pressure for 30 seconds then release.
- After a 30 second rest period, repeat the penile modelling technique for a total of 3 modelling attempts at 30 seconds for each attempt.

The patient should then be instructed to self-perform penile modelling activities at home each day for the 6-week period following the physician penile plaque modelling visit of each treatment cycle, according to the detailed instructions provided in the package leaflet.

ANNEX IV

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR THE VARIATION TO THE TERMS OF THE MARKETING AUTHORISATION(S)

Scientific conclusions

Taking into account the PRAC Assessment Report on the PSUR(s) for collagenase *clostridium histolyticum*, the scientific conclusions of the CHMP are as follows:

The review of data presented in the PSUR for Xiapex, covering the period from 28 February 2018 to 27 February 2019, identified post-marketing and literature case reports of finger necrosis and/or amputation and of finger fractures in patients with Dupuytren's contracture treated with collagenase *clostridium histolyticum*. Taking into account the plausibility of the mechanism of collagenase *clostridium histolyticum* and the subsequent manipulation procedure in patients with Dupuytren's contracture, the PRAC considers that the product information for Xiapex should be updated to include a warning with regards to finger necrosis resulting in some cases in finger amputation and a warning with regards to finger fracture should be included in section 4.4 of the SmPC. Reduced peripheral circulation may be one contributing factor for finger necrosis. For patients with an increased risk of fracture, e.g. patients with osteopenia/osteoporosis, special caution is needed during the manipulation procedure. The section 4.8 of the SmPC is updated to include the adverse reactions "digital necrosis" and "digital fracture" with a frequency "not known". The package leaflet is updated accordingly.

In addition, based on the review of post marketing case reports of penile fracture in patients with Peyronie's disease, the PRAC considers that the product information for Xiapex should be updated to include a new wording for section 4.4 of the SmPC and section 2 of the PIL to increase the minimum time span between injection and resumption of sexual activity to at least 4 weeks and to be cautious when resuming sexual activity.

The CHMP agrees with the scientific conclusions made by the PRAC.

Grounds for the variation to the terms of the Marketing Authorisation

On the basis of the scientific conclusions for collagenase clostridium histolyticum the CHMP is of the opinion that the benefit-risk balance of the medicinal product(s) containing collagenase *clostridium histolyticum* is unchanged subject to the proposed changes to the product information.

The CHMP recommends that the terms of the Marketing Authorisation should be varied.