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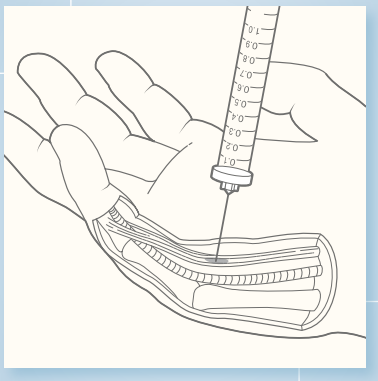
XIAPEX®▼

collagenase clostridium histolyticum

Injection Training Brochure

The following training brochure is designed to ensure appropriate treatment of patients with Dupuytren's contracture with Xiapex.



▼ This medicinal product is subject to additional monitoring.

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Dupuytren's disease and hand anatomy

Dupuytren's disease is a slowly progressive connective tissue disorder that affects the palmar fascia of the hand. It can lead to flexion contractures at the digital joints, resulting in significant functional impairment and disability.

During the initial proliferative stage of the disease, fibroblasts transform into myofibroblasts, with accompanying collagen deposition and nodule formation. The subsequent involutional stage involves alignment of myofibroblasts along the lines of tension. Nodules thicken, cords form and contractures start to develop. In the final residual phase the myofibroblasts disappear, leaving thick bands of collagen and progressive contractures.

The joints most commonly affected in Dupuytren's disease are the metacarpophalangeal joint (MP) and the proximal interphalangeal joint (PIP), with the ring and little fingers most frequently presenting with a contracture. Involvement of the thumb and index finger is not uncommon, but usually milder. The disease is often bilateral and can affect multiple fingers.

Overview of hand anatomy[1–4]

The palmar fascial complex is the centre of activity in Dupuytren's disease. It comprises five anatomical components: the radial (thenar) aponeurosis (RA), the ulnar (hypothenar) aponeurosis (UA), the central (palmar) aponeurosis (PA), the palmo-digital fascia and the digital fascia (Figure 1).

The palmar aponeurosis consists of three types of fibres: longitudinal fibres, transverse fibres and vertical, or superficial, fibres.

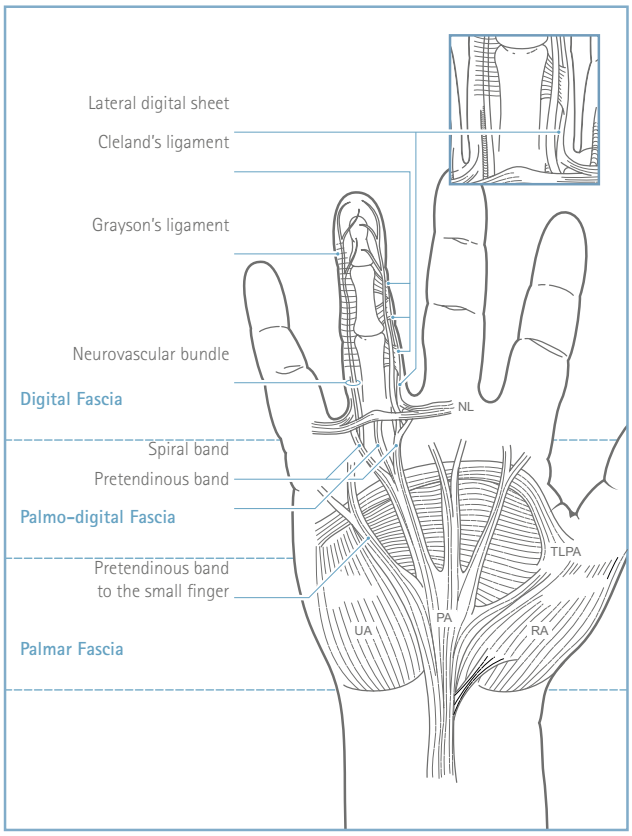
The vertical fibres run obliquely toward the skin and at the metacarpal heads give rise to the distal palmar crease. The tight attachment of these fibres to the skin produces the dimpling of the palmar skin that is often seen in Dupuytren's. The longitudinal fibres form structures that are called bands.

The palmar fascia

The longitudinal fibres fan out and separate into four pretendinous bands at the level of the head of the four metacarpal bones which lead to the 2nd, 3rd, 4th and 5th digits. Another, shorter pretendinous band extends to the thumb, but it is weak and not always present.

At the distal edge of the metacarpals (in the palmo-digital fascia), the pretendinous longitudinal fibres terminate and separate into 3 layers (Figure 2). The deep layer passes dorsally and almost vertically. The superficial layer attaches to the skin at the palmar digital crease (the crease at the base of the finger on the volar side of the hand).

Figure 1. The palmar fascial complex



The digital fascia

The central layer of the pretendinous longitudinal fibres bifurcates into two bands which extend onto each side of the flexor tendons. These travel distally and dorsally to form the web space coalescence, passing deep to the natatory ligament (Figure 1). The fibres rotate 90 degrees and emerge distally to the natatory ligament (NL), then continue as the lateral digital sheets.

1. Rayan G. *Hand Clin* (1999) **15(1)**:73–86.
2. Hughes TB. *et al. J Am Soc Surg Hand* (2003) **3(1)**:27–40.
3. Townley *et al. BMJ* (2006) **332**;397–400.
4. McGrouther DA, *Hand* (1982) **14(3)**:215–236.

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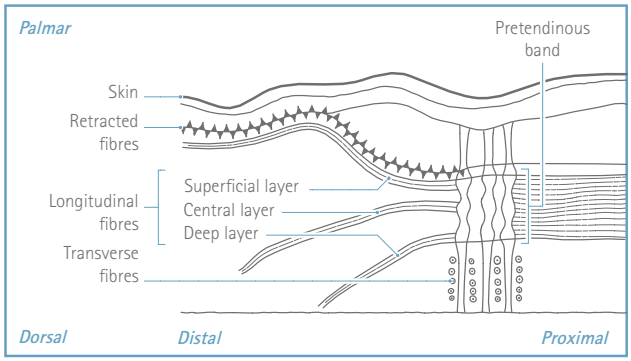
Figure 2. Longitudinal fibres in the fascia

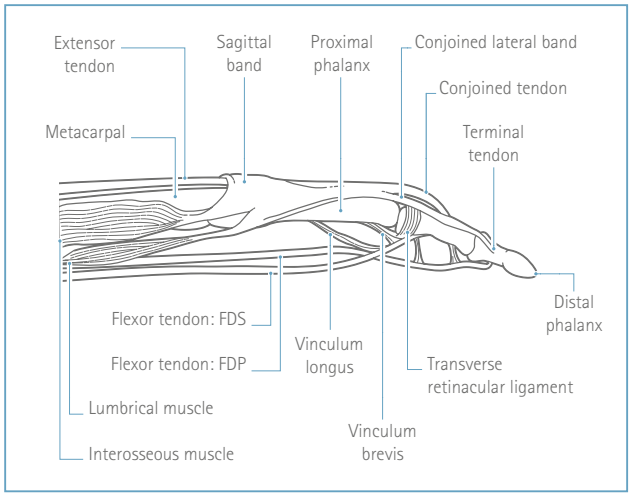


These sheets are lateral to the neurovascular bundle. Coronal fibres project from the lateral digital sheets on each side of the neurovascular bundle at the volar side (Grayson's ligament) and dorsal side (Cleland's ligament). It is important to note that the neurovascular bundle lies deep to the palmar fascia and becomes more superficial when it approaches the fingers.

Digital flexors

The primary flexors of the digit are the flexor digitorum profundus (FDP) and the flexor digitorum superficialis (FDS) tendons (Figure 3).

Figure 3. The flexor and extensor apparatus



At the MP joint, the FDS tendon enters the digital flexor sheath with the FDP tendon. Once within the sheath, the FDS tendon starts to flatten. At the proximal third of the proximal phalanx it splits and passes around the FDP tendon, to reunite deep to the FDP tendon.

The FDS tendon continues dorsally to its insertion point at the volar base of the middle phalanx. At the level of the PIP joint, the FDP tendon is palmar to the FDS tendon and continues distally to the level of the distal interphalangeal (DIP) joint. There it inserts broadly onto the base of the proximal volar third of the distal phalanx.

The flexor sheath comprises of pulleys which keep the flexor tendons close to the centre of rotation, thus helping to control flexion in the digits.

Pathoanatomy of Dupuytren's disease[1–3]

In Dupuytren's disease normal fascia bands develop into cords, which shorten and lead to contractures of the MP, PIP and, sometimes, DIP joints. As well as causing contractures, some cords can displace neurovascular structures, putting them at risk of damage during corrective surgery or percutaneous needle fasciotomy.

Skin pits form in the palm between the distal palmar crease and the palmar digital crease, owing to contracture of the superficial layer of the pretendinous band that inserts into the skin.

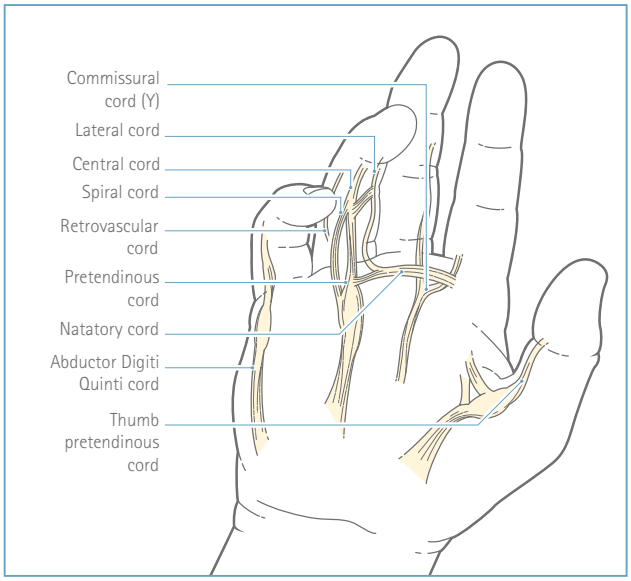
Types of cords

Several main types of cords have been identified, although substantial variability has been observed: the pretendinous cord, the natatory cord, the spiral cord, the central cord and the lateral cord (Figures 4 and 5).

The pretendinous cord is the cord that is most commonly seen in Dupuytren's disease and derives from the pretendinous band. It typically causes MP contractures.

The natatory cord develops from the natatory ligament and can produce contractures of the 2nd, 3rd and 4th web spaces, limiting abduction.

Figure 4. Dupuytren's cords



1. Rayan G. *Hand Clin* (1999) **15(1)**:73–86.
2. Hughes TB. *et al. J Am Soc Surg Hand* (2003) **3(1)**:27–40.
3. Townley *et al. BMJ* (2006) **332**;397–400.

The spiral cord can develop from the pretendinous band, the lateral digital sheet and Grayson's ligament. It leads to contractures of the MP and PIP joints, usually in the 5th finger, but also in the other fingers. In the palm, the spiral cord is superficial to the neurovascular bundle. In the digit, it spirals around the bundle in the early stages of Dupuytren's disease but, as the fascia thickens and contracts, it becomes straighter. This leads to the displacement of the neurovascular bundle, (which now coils around the cord), to the midline of a finger. The greater the contracture of the spiral cord, the more the neurovascular structures are displaced superficially and towards the midline, putting them at risk of injury during surgery or percutaneous needle fasciotomy.

Although it occurs less frequently, another important consideration is the so called "spiral nerve". In some cases spiral cords, particularly those which originate deep in the palm, may cross under the neurovascular bundle or the digital nerve only (due to its more proximal division than the accompanying artery) displacing it proximally and towards the midline. This can sometimes be indicated by a circular area of pulpy, soft 'redundant skin' in the palm on either side of the cord at the level of MP joint. Similar phenomenon has been observed for axial digitopalmar cords (e.g. central cords). This is also important to identify prior to any corrective procedure.

The central cord usually has no fascial precursor and is usually an extension of the pretendinous cord to the fingers. It occurs in the midline and attaches into the flexor tendon sheath near the PIP joint. It does not usually displace the neurovascular bundle.

Lateral cords originate from the lateral digital sheet and attach to the skin or the flexor tendon sheath near Grayson's ligament. These result in PIP contractures and sometimes contractures of the DIP joints. Owing to their volume, lateral cords can displace the neurovascular bundle to the midline.

Other types of cord may also occur.

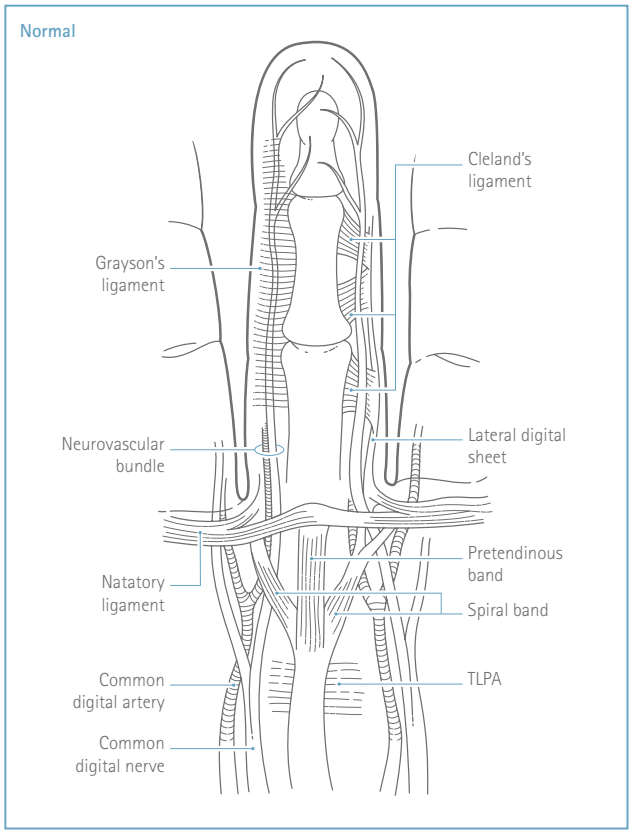
The abductor digiti quinti cord, or isolated digital cord, forms in the 5th finger from the abductor digiti quinti muscle. It runs superficially to the neurovascular bundle, but may occasionally trap and displace it.

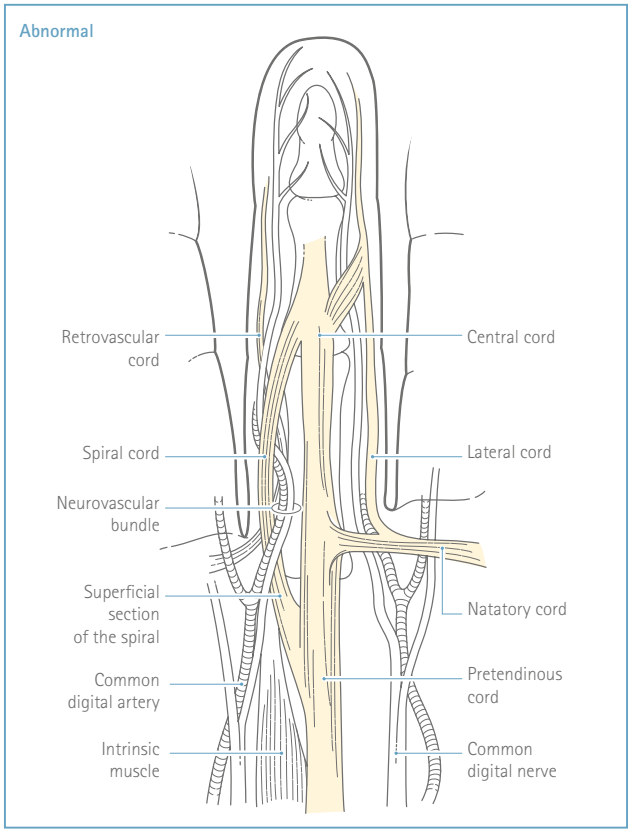
Retrovascular cords may sometimes present, but are poorly defined and thought to originate from the retrovascular band, located deep to the neurovascular bundle. They do not cause PIP contractures.

Commissural cords may form in the thumbs from the distal commissural ligament (the radial extension of the natatory ligament) and the proximal commissural ligaments (the radial extension of the transverse ligament of the palmar aponeurosis). Both of these cords cause contracture of the first web space. A pretendinous cord in the thumb is uncommon, but if present can cause flexion deformity of the thumb MP joint.

The differences between the normal and abnormal finger anatomy are depicted below (Figure 5). These diagrams demonstrate the pathological changes that occur in the development of Dupuytren's disease in the finger.

Figure 5. Anatomy of the finger





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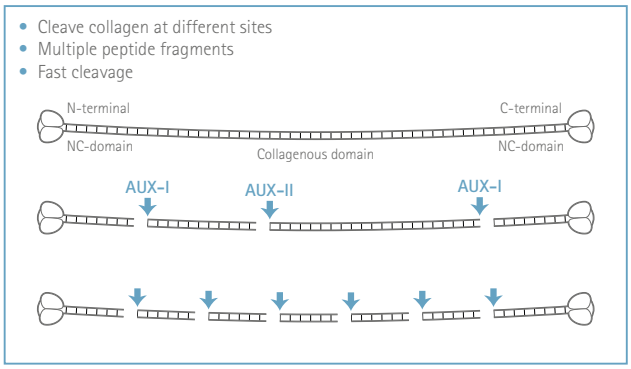
All diagrams from this section have been redrawn based on the publications listed on page 2.

Xiapex

Xiapex (collagenase clostridium histolyticum) was developed as a targeted therapy for the treatment of patients with Dupuytren's contracture presenting with a palpable cord. Xiapex is composed of two distinct collagenases that are isolated and purified from the bacterium *Clostridium histolyticum*. The pharmacologic activity involves selective lysis of collagen at the site of injection (i.e. the Dupuytren's cord). Its therapeutic activity is thus localised and therefore does not require systemic exposure to be effective. The two collagenases work in a complementary fashion to cleave the collagen chains and disrupt the pathologic collagen cords that cause Dupuytren's contractures. AUX-I (a class I collagenase) cleaves the terminal portions of the collagen chain and AUX-II (a class II collagenase) cleaves the interior segment of the collagen chain (Figure 6).

Dupuytren's cords are composed primarily of types I and III collagen, which are substrates for both the collagenases AUX-I and AUX-II. Other soft tissues of the hand, including ligaments and tendons, are also susceptible to the action of these collagenases, making it necessary for the treating physician to understand the mechanism of action and the appropriate administration procedure of Xiapex. Importantly, the supporting structures of nerves, arteries and veins are composed primarily of type IV collagen, which is resistant to the action of Xiapex.[5]

Figure 6. Xiapex mechanism of action



This reference booklet provides the necessary information to:

- Prepare Xiapex for injection
- Inject it into a cord overlying the affected MP or PIP joint
- Perform the finger extension procedure for disrupting the cord
- Provide appropriate post-procedural care to patients who have been treated with Xiapex

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

5. FDA Submission dossier. Auxilium Pharmaceuticals 2009.

Information to share with patients

It is important that, prior to Xiapex administration, the physician ensures that patients clearly understand the following information.

Procedures to be performed and the desired treatment outcome

Treatment with Xiapex consists of an injection, followed 24-72 hours after injection by a finger extension procedure to disrupt the Dupuytren's cord. In some cases satisfactory outcome can be achieved after just one injection. However, in other instances more than one treatment may be required per cord. Up to a maximum of 3 injections can be performed to the same cord at 4 week intervals, if the cord has not ruptured.

Local anaesthesia may be an option during the finger extension procedure at the physician's discretion and in discussion with the patient.

It is important to mention that, even with successful disruption of a treated cord, there can be recurrence of the contracture.

Precautions for use in patients receiving concomitant medications

Xiapex must be used with caution in patients with coagulation disorders or those taking anticoagulants. 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.

Caution should be used when administering Xiapex in patients receiving concomitant flouroquinolone antibiotics (ciprofloxacin, norfloxacin, ofloxacin, gatifloxacin, gemifloxacin, levofloxacin and moxifloxacin) due to a potentially higher risk for tendon injury associated with concomitant fluorquinolone use.

Treatment with Xiapex is not recommended in patients who have received tetracycline antibiotics within 14 days prior to receiving an injection.

Precautions during pregnancy

Female patients should be made aware that the use of Xiapex is not recommended in pregnancy and treatment should be postponed until after pregnancy.

Contraindications

Xiapex is contraindicated in patients with previous hypersensitivity to collagenase or any of the product excipients.

Adverse reactions associated with the treatment

There are some common local adverse reactions that are likely to be experienced after injection and/or the finger extension procedure. The most common of these reactions are local swelling, bruising and pain around the injection site of the treated hand. The majority of these reactions resolve within two weeks after injection. These local reactions are expected and local reactions do not necessarily indicate an unsuccessful procedure or any permanent injury to the hand.

During the finger extension procedure, patients with skin adherent to the treated cord may experience skin tearing as the cord ruptures. If skin tearing occurs, standard wound care should be administered.

Serious adverse reactions associated with the treatment

Serious side effects, such as tendon injury, tendon rupture and ligament injury, although uncommon, can occur.

Patients should be instructed to promptly contact their doctor if there is evidence of infection or symptoms of tendon rupture.

Potential risks

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.

There is also a theoretical risk of reactions related to cross-reactivity with endogenous human matrix metalloproteinases (MMPs) (including the development of a musculo-skeletal syndrome and the development or exacerbation of autoimmune disorders) although clinical evidence of this has not been observed.

For more safety information, please refer to the last section of the brochure.

Xiapex preparation for administration

Xiapex dosing

The dose of Xiapex to be administered is 0.58 mg per injection.

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

Xiapex must be carefully reconstituted prior to use, using aseptic technique. Before reconstituting, check the package expiry to ensure it is within date. It is important to note that Xiapex is reconstituted using different amounts of sterile diluent, depending on whether the injection is into a cord contracting an MP or PIP joint.

Each vial of Xiapex and sterile solvent for reconstitution should only be used for a single injection. If cords of two 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.

Reconstitution of Xiapex

Xiapex is supplied in single-use glass vials containing 0.9 mg of sterile, lyophilised powder for reconstitution (Figure 7). Each vial of Xiapex should be reconstituted with the sterile diluent that is provided in the packet.

The diluent consists of 2 mM calcium chloride in 0.9% sodium chloride USP (0.03% calcium chloride in 0.9% sodium chloride USP).

The package containing Xiapex and the diluents should be kept refrigerated between 2°C and 8°C. Before reconstitution, the vials of Xiapex and diluent should be removed from the refrigerator and allowed to stand at room temperature (20 to 25°C), for at least 15 minutes, but no longer than 60 minutes.

Once the vials have been allowed to stand at room temperature, please follow the reconstitution protocol overleaf (Figure 8).

The reconstituted solution of Xiapex should be clear. Inspect the solution for particulate matter and discolouration prior to injection. If the solution is cloudy, DO NOT inject Xiapex.

Reconstituted Xiapex can be kept at room temperature (20 to 25°C) for up to one hour, or refrigerated at 2°C to 8°C for up to four hours, prior to administration. If refrigerated, the solution must be allowed to return to room temperature for approximately 15 minutes before use.

Figure 7. Diluent and Xiapex vials

Before Xiapex is reconstituted, the person responsible for preparing the solution should ensure that the following are easily accessible in the treatment room:

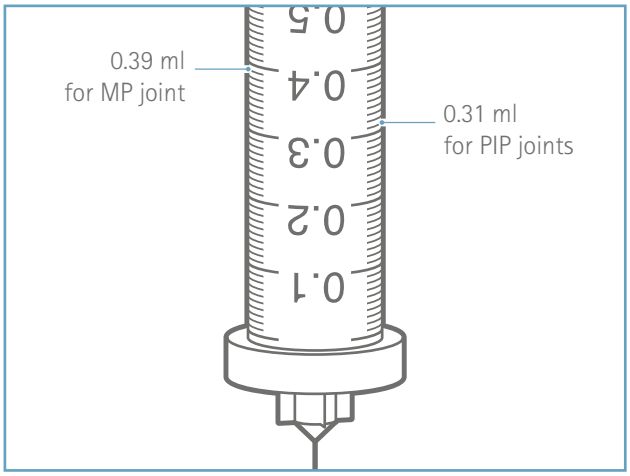
1. Two hubless syringes with 0.01ml graduations and a permanently fixed 12 or 13 mm, 26 or 27 gauge needle – one is for reconstitution of Xiapex and one is for the injection of Xiapex.
2. Emergency medication for treatment of potential allergic reactions (an adrenaline injection kit and antihistamine medication for treatment of potential allergic reactions).
3. Dressing for the patient's finger post-injection.
4. A copy of this training brochure which contains instructions for the preparation, injection and finger extension procedure.

Xiapex reconstitution protocol

Figure 8. Xiapex reconstitution protocol

All steps for reconstitution of Xiapex should be carried out using aseptic technique, with sterile alcohol, and in line with current, local, standard of care. Before reconstituting Xiapex, check that the package is within date.

Confirm the cord to be treated and appropriately mark the area to prevent misapplication



Cord contracting the metacarpophalangeal (MP) joint

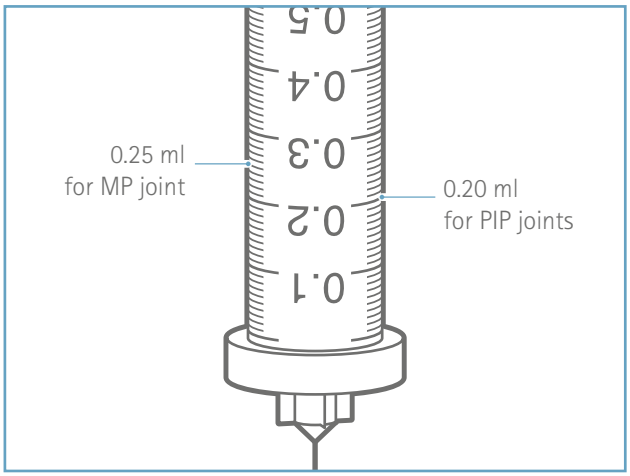
Withdraw 0.39 ml of the diluent using a syringe

Cord contracting the proximal interphalangeal (PIP) joint

Withdraw 0.31 ml of the diluent using a syringe

Inject the diluent slowly into the vial containing the Xiapex. Discard the syringe and remaining diluent

Agitate gently by swirling the mixture slowly, ensuring all Xiapex powder is dissolved.
DO NOT INVERT THE VIAL OR SHAKE THE SOLUTION
ONLY INJECT IF SOLUSION IS CLEAR



Cord contracting the MP joint

Withdraw 0.25 ml of the solution using a syringe

Cord contracting the PIP joint

Withdraw 0.20 ml of the solution using a syringe

Inject according to injection protocol in this brochure

Treating cords affecting MP joints

Please note that reconstitution volumes and injection volumes differ depending on which joint the cord to be treated is contracting.

For cords contracting MP joints each dose should be reconstituted using 0.39 ml of diluent. The injection volume for cords contracting MP joints is 0.25 ml.

Table 1. Reconstitution volume for MP joint

Reconstitution of Xiapex single-use vial		
Joint to be treated	Sterile diluent required for reconstitution	Injection volume to deliver 0.58 mg of Xiapex
MP joint	0.39 ml	0.25 ml

Xiapex injection procedure

STEP 1
Selecting and preparing the injection site

The optimal injection site is the point where the cord is furthest away from the underlying flexor tendon. Usually this is at the point of maximum 'bowstring' of the cord. The injection site must be at a point where the cord is not intimately adherent to the skin (Figure 9) to facilitate proper administration and decrease the risk of skin tearing during the finger extension procedure.

Reconfirm the cord to be treated and ensure that the area is appropriately marked. The choice of injection site should take into account the probable position of other non-targeted structures within the hand, to minimise the exposure risk of tendons and ligaments to Xiapex. Recommended injection sites for cords contracting MP joints are shown in Figure 10.

Note that in cases where both the MP and PIP joint are affected in the same digit, the cord affecting the MP joint should be treated initially, as successful disruption of the MP cord can decrease PIP contracture in the treated digit.

Just prior to administration of Xiapex, the skin at the injection site should be prepared with a suitable antiseptic and allowed to dry.

Administration of a local anaesthetic agent prior to injection of Xiapex is NOT recommended as it may interfere with the ability to detect paresthesia in cases where the needle has been inserted into a nerve.

Figure 9. Injection site selection – skin adherence to the cord in an MP joint contracture

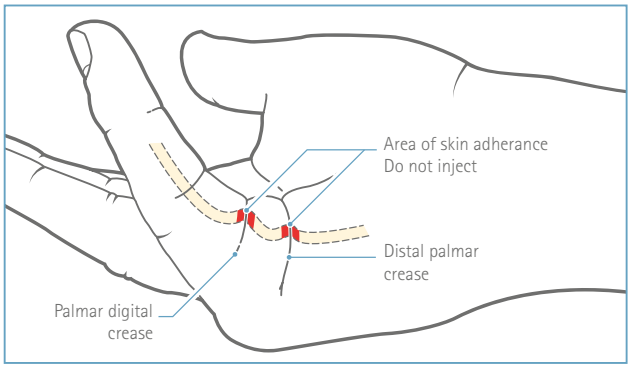
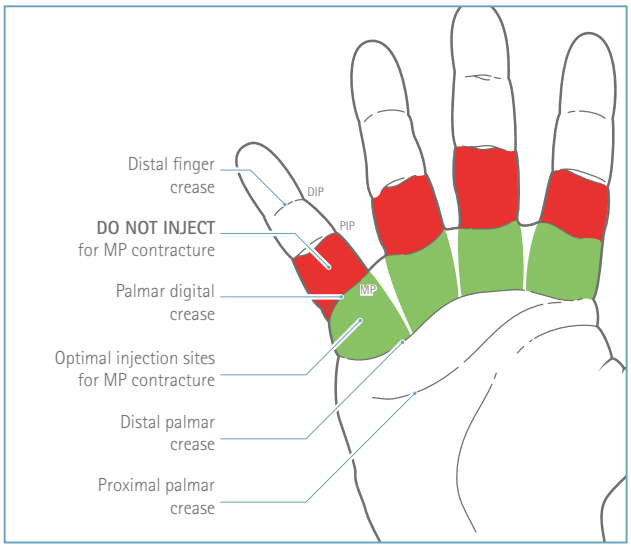


Figure 10. Injection site selection – MP joint contractures



STEP 2
Inserting the needle

Withdraw 0.25 ml of reconstituted Xiapex using a second hubless syringe.

Insert the tip of the needle into the selected cord, taking care to keep the needle within the cord (Figure 11). Appropriate placement can be identified by the cord's increased resistance and gritty consistency. Avoid passing the needle tip through the cord, to minimise the possibility of injecting Xiapex into neighbouring tissues. The needle insertion should be no deeper than 2-3 mm. It may not be possible to feel a change in consistency as you pass through the cord, so the depth of the needle may be a helpful guide.

If the insertion of the needle causes paresthesia or the needle is suspected to be in the tendon, withdraw the needle and reposition it into the cord. If placement of the needle is in question, ask the patient to slowly and carefully flex and extend the treated finger a few degrees at the DIP and PIP joints. If this causes movement of the needle then it is likely to be in the tendon and should be withdrawn and repositioned.

STEP 3
Xiapex administration

After confirming that the needle is within the cord, depress the plunger of the syringe, taking care not to push the tip of the needle through the cord. One-third of the total dose should be injected into the first injection site. If the needle is in the proper location, there will be some resistance noted during the injection procedure.

Withdraw the needle tip from the cord, keeping the needle tip under the skin, and reposition it to a slightly more distal location (approximately 2-3 mm) and, after ensuring the tip of the needle is within the cord, inject another one-third of the dose (Figure 12).

Again, withdraw the needle tip from the cord, keeping the needle in the hand, and reposition it a third time proximal to the initial injection (approximately 2-3 mm); after ensuring the tip of the needle is within the cord, inject the final one-third of the dose (Figure 12).

In cases where the subject has a Y-shaped commissural cord, created by combination of a central and a natatory cord, the injection should be made at the bifurcation of the cord (Figure 13).

Figure 11. Location of the injection

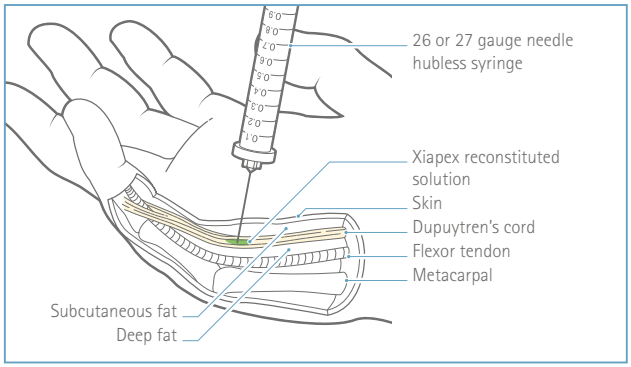


Figure 12. Injection target sites

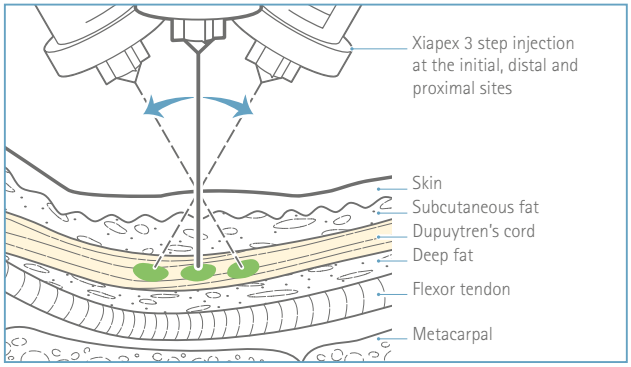
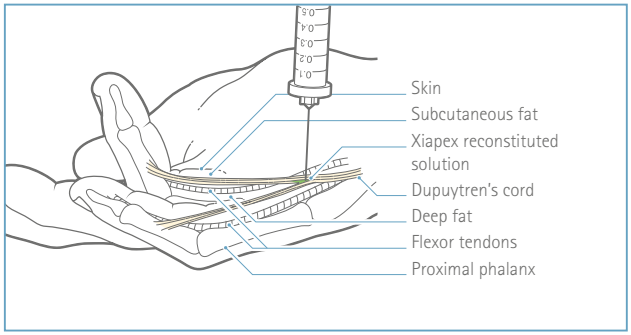


Figure 13. Image detailing the injection site for Xiapex into a Y-shaped cord



Discard the unused portion of the Xiapex reconstituted solution after injection and do not store, pool, or re-use.

Treating cords affecting PIP joints

Please note that reconstitution volumes and injection volumes differ depending on which joint the cord to be treated is contracting.

For cords contracting PIP joints each dose should be reconstituted using 0.31 ml of sterile diluent. The injection volume for cords contracting PIP joints is 0.20 ml.

Table 2. Reconstitution volume for PIP joint

Reconstitution of Xiapex single-use vial		
Joint to be treated	Sterile diluent required for reconstitution	Injection volume to deliver 0.58 mg of Xiapex
PIP joint	0.31 ml	0.20 ml

Xiapex injection procedure

Care and attention 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.

STEP 1
Selecting and preparing the injection site

The optimal injection site is the point where the cord is furthest away from the underlying flexor tendon. Usually this is at the point of maximum 'bowstring' of the cord. The injection site must be at a point where the cord is not intimately adherent to the skin (Figure 14) to facilitate proper administration and decrease the risk of skin tearing during the finger extension procedure.

Reconfirm the cord to be treated and ensure that the area is appropriately marked. The choice of injection site should take into account the probable position of other non-targeted structures within the hand, to minimise the exposure risk of tendons and ligaments to Xiapex. Recommended injection sites for cords contracting PIP joints are shown in Figure 15.

Note that in cases where both the MP and PIP joint are affected in the same digit, the cord affecting the MP joint should be treated initially, as successful disruption of the MP cord can decrease PIP contracture in the treated digit.

Just prior to administration of Xiapex the skin at the injection site should be prepared with a suitable antiseptic and allowed to dry.

Administration of a local anaesthetic agent prior to injection of Xiapex is NOT recommended as it may interfere with the ability to detect paresthesia in cases where the needle has been injected into a nerve.

When treating a cord at the PIP joint, care should be taken to inject as close as possible to the palmar digital crease – no more than 4 mm distal to this crease (Figure 15). Therefore the point of maximum 'bowstring' of the cord within this area should be selected. **This is particularly important for cords situated at the PIP joint of the fifth finger to reduce the risk of tendon or ligament injury.**

Figure 14. Injection site selection – skin adherence to the cord in a PIP joint contracture

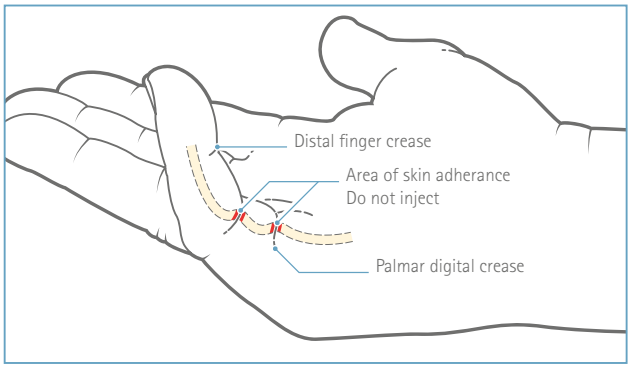
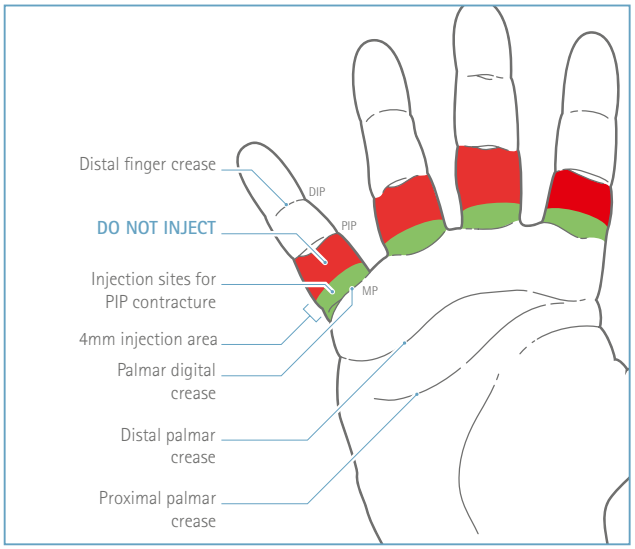


Figure 15. Injection site selection – PIP joint contractures



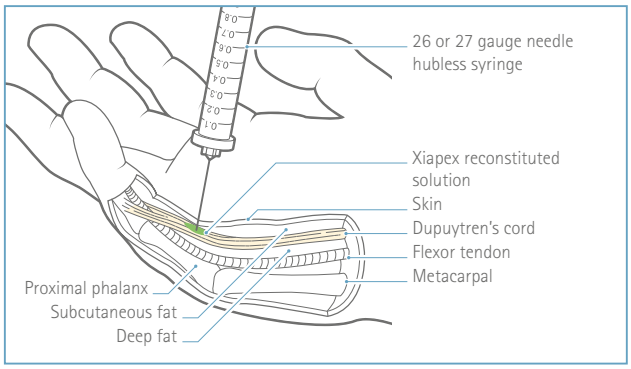
STEP 2
Inserting the needle

Withdraw 0.20 ml of reconstituted Xiapex using the second hubless syringe.

Insert the tip of the needle into the selected cord, taking care to keep the needle within the cord (Figure 16). Appropriate placement can be identified by the cord's increased resistance and gritty consistency. Avoid passing the needle tip through the cord, to minimise the possibility of injecting Xiapex into neighbouring tissues. The needle insertion should be no deeper than 2-3 mm. It may not be possible to feel a change in consistency as you pass through the cord, so the depth of the needle may be a helpful guide.

If the insertion of the needle causes paresthesia or the needle is suspected to be in the tendon, withdraw the needle and reposition it into the cord. If placement of the needle is in question, ask the patient to slowly and carefully flex and extend the treated finger a few degrees at the DIP and PIP joints. If this causes movement of the needle then it is likely to be in the tendon and should be withdrawn and repositioned.

Figure 16. Location of the injection



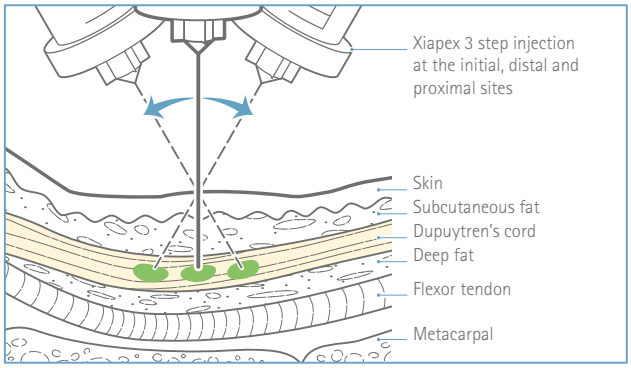
STEP 3
Xiapex administration

After confirming that the needle is within the cord, depress the plunger of the syringe, taking care not to push the tip of the needle through the cord. One-third of the total dose should be injected into the first injection site. If the needle is in the proper location, there will be some resistance noted during the injection procedure.

Withdraw the needle tip from the cord, keeping the needle tip under the skin, and reposition it to a slightly more distal location (approximately 2-3 mm) and, after ensuring the tip of the needle is within the cord, inject another one-third of the dose (Figure 17).

Again, withdraw the needle tip from the cord, keeping the needle in the hand, and reposition it a third time proximal to the initial injection (approximately 2-3 mm); after ensuring the tip of the needle is within the cord, inject the final one-third of the dose (Figure 17).

Figure 17. Injection target sites



Discard the unused portion of the Xiapex reconstituted solution after injection and do not store, pool, or re-use.

Xiapex injection aftercare and patient observation

Upon completion of the injection procedure, place a bulky dressing over the treated hand and instruct the patient to limit motion and refrain from use of the injected hand. They should be advised not to flex or extend the fingers of the injected hand, to reduce extravasation of Xiapex out of the cord.

They should also be informed not attempt to disrupt the injected cord by self-manipulation and should elevate the injected hand as much as possible until the day after the finger extension procedure.

After injection, the patient should be observed for potential adverse reactions including anaphylaxis or systemic hypersensitivity (see symptoms opposite). After the observation period (30 minutes), the patient may leave the clinic providing he/she is stable and has exhibited no sign of systemic hypersensitivity or other systemic adverse reactions.

The patient should be instructed to return approximately 24-72 hours after injection for the passive finger extension procedure.

Potential symptoms of hypersensitivity or impending anaphylaxis:

- Repeated sneezing
- Generalised erythema, pruritus, or paresthesia
- Localised or generalised angioedema
- Difficulty breathing
- Neck or chest tightness
- Dizziness
- Syncope

Xiapex finger extension procedure and outpatient treatment

24–72 hours post injection

Since the injection some patients may have experienced a spontaneous rupture of the cord before their follow-up visit. If this has not occurred, a finger extension procedure will need to be performed in order to help facilitate rupture of the cord.

Local anaesthesia may be used at the physician's discretion during the finger extension procedure. The force exerted during extension of the finger should be uniform and persistent to the extent of the patient's pain threshold. Direct pressure to the site of the injection should be avoided as it will still be tender (Figures 18 and 19). Finger extension should be performed for approximately 10-20 seconds. During the finger extension procedure, patients with skin adherent to the treated cord may experience skin tearing as the cord ruptures. If skin tearing occurs, standard wound care should be administered.

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.

If the first finger extension procedure does not successfully rupture the cord, a second and third attempt can be made at 5-10 minute intervals as necessary. No more than three finger extension procedures per cord should be attempted during one follow-up visit.

If manipulating a PIP joint the MP joint should be held in flexed position to isolate the forces of the extension procedure on the cord affecting the PIP joint.

If the cord has not ruptured after three attempts, a subsequent clinic visit should be scheduled approximately four weeks later. If the cord causing the contracture remains intact, the patient can receive another treatment cycle of Xiapex, up to a maximum of three cycles (Figure 20).

Figure 18. Finger extension 1

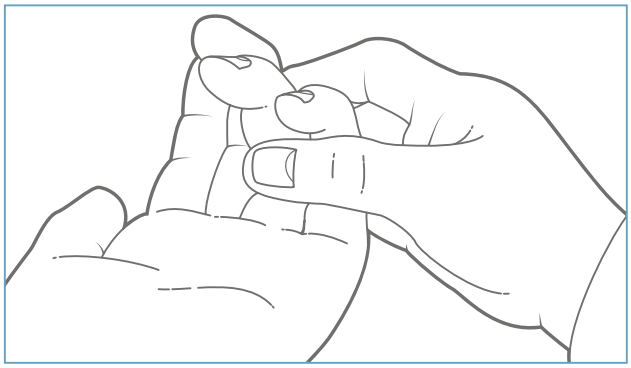


Figure 19. Finger extension 2

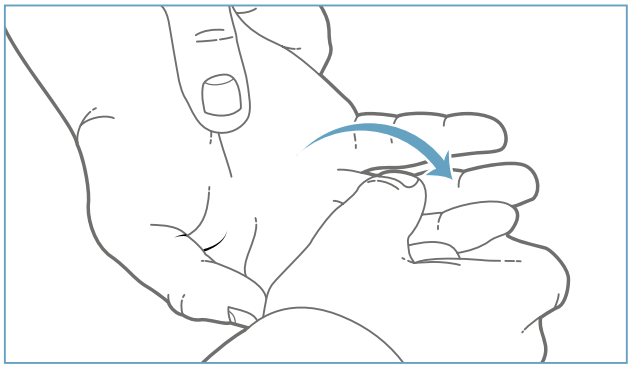
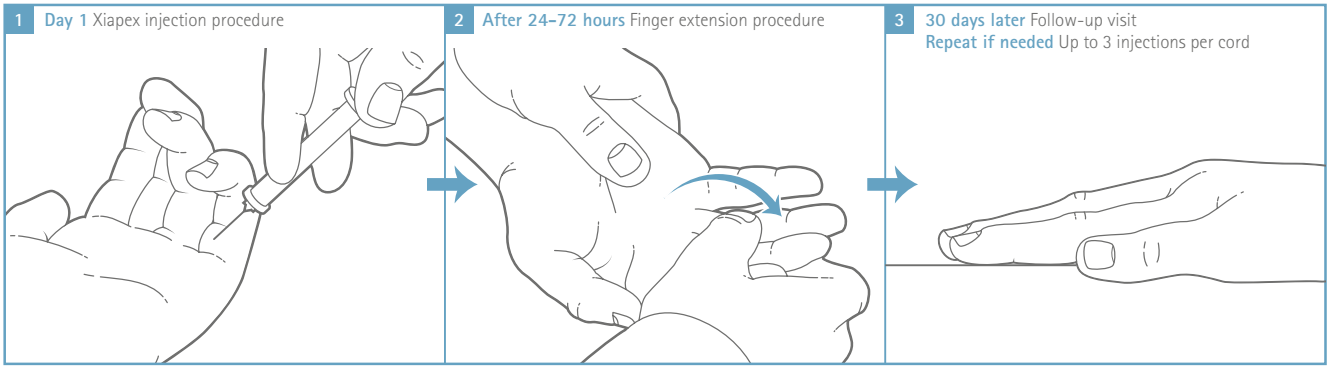


Figure 20. Repeated cycles of treatment



Post Day 1 follow up

Splinting is recommended following the finger extension procedure since, in the clinical development programme, patients were fitted for a splint to be worn at bedtime for up to four months.

Patients should also be instructed to carry out finger extension and flexion exercises at home. They should be encouraged to return to their normal daily activities, but not to undertake strenuous activities until advised.

Standard analgesia, wound care and management of bruising/swelling should apply to all patients, in keeping with the local standard of care.

Xiapex indication and important safety information

Xiapex (collagenase clostridium histolyticum) is indicated for the treatment of Dupuytren's contracture in adult patients with a palpable cord.

Warnings and Precautions

Allergic reaction potential

Xiapex is contraindicated in patients with previous hypersensitivity to the collagenase or any of the product excipients.

Physicians should be prepared for any potential allergic reactions that may occur immediately following the injection, and medication should be available for use in the event of a systemic allergic reaction. After receiving Xiapex, patients can be discharged if there is no sign of systemic hypersensitivity or anaphylaxis.

Injection precaution

Care should be taken to ensure that Xiapex is injected into the pathological cord causing the contracture and not into the surrounding tissues. An injection into any structures containing collagen can result in damage that can be permanent in some cases, such as tendon rupture and ligament injury. If tendon or ligament injury is suspected, the patient should be fitted with a splint and follow-up with an appropriate surgical specialist should be arranged.

Follow the injection procedure carefully to reduce the risk of tendon rupture or ligament injury.

Use in patients with coagulation disorders

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 has not been studied and therefore is not recommended. Xiapex must be used with caution in patients with known coagulation disorders.

Interaction with other medicinal products and other forms of interaction

The use of Xiapex in patients who have received tetracycline antibiotics within 14 days is not recommended.

Pregnancy

Female patients should be made aware that the use of Xiapex is not recommended during pregnancy, and treatment should be postponed until after pregnancy.

Adverse reactions

In the clinical development programme of Xiapex (n=1082), nearly all patients experienced adverse reactions associated with administration of Xiapex and/or to the finger extension procedure to disrupt the cord. The majority of these adverse reactions were local reactions of mild to moderate severity, which resolved within two weeks post-injection.

The most commonly reported adverse events included oedema peripheral (localised to the treated extremity), contusion, injection site pain, pain in the extremity and injection site haemorrhage (manifested as bruising rather than frank bleeding).

Some subjects reported skin lesions (tearing of adherent skin overlying the cord) occurring during the finger extension procedure. Caution should therefore be exercised in patients with Dupuytren's cords that adhere to the skin, as they 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.

The incidence of skin laceration (29.1%) was higher for subjects treated with two concurrent injections of Xiapex in 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, n=249) (skin laceration 8.8%). 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 (ie, most adverse events were local to the treated extremity and of mild or moderate intensity).

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.

Table 3 lists adverse reactions that occurred in >5% of the patients in the clinical development programme.

XIAPEX®
collagenase clostridium histolyticum

5. FDA submission dossier. Auxilium Pharmaceuticals 2009.

Table 3. Adverse reactions associated with Xiapex[5]

Adverse Reaction	Xiapex (n=1082)
Oedema peripheral	76.7%
Contusion	54.2%
Injection site pain	40.6%
Pain in extremity	35.8%
Injection site haemorrhage	34.0%
Tenderness	28.5%
Injection site swelling	24.5%
Ecchymosis	17.9%
Pruritus	12.5%
Skin laceration	10.9%
Lymphadenopathy	10.9%
Blood blister	9.0%
Axillary pain	6.7%
Injection site pruritus	5.3%
Haematoma	5.2%

As expected when foreign proteins are injected into human tissues, an antibody response is elicited. In the clinical programme, one month after the first injection of Xiapex most of the subjects had antibodies detected against both AUX-I and 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. No apparent correlation of antibody development to clinical response or adverse reaction was observed.

There is a theoretical risk of interference between anti drug antibodies against Xiapex and human matrix metalloproteinases. However, adverse events indicating the development or exacerbation of autoimmune disease or the development of a musculoskeletal syndrome (MSS) have not been observed in the clinical programme. If it were to develop, MSS would occur progressively and is characterised 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.

Serious adverse reactions

The majority of serious adverse reactions reported in patients treated with Xiapex were confined to the treated hand. These included three cases of tendon rupture and one case of pulley injury. All these cases occurred with contractures at the level of the PIP joint of the fifth finger. There was also one case of tendonitis reported.

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.

In addition, one case each of complex regional pain syndrome and sensory abnormality of the treated hand occurred.

These serious adverse reactions were uncommon in the clinical programme, with a frequency of ≥1/1000 and ≤1/100.

In the post-marketing clinical study AUX-CC-867 one case of an anaphylactic reaction was reported in a patient who had previous exposure to Xiapex for the treatment of Dupuytren's contracture.

Adverse reaction reporting

Any adverse reactions considered related to Xiapex should be documented and reported immediately.

Please contact your local Sobi office for further information on reporting adverse reactions. See box below prescribing information overleaf.

Note: An inverted black triangle denotes that special reporting is required in relation to adverse reactions. Healthcare professionals are asked to report all suspected adverse drug reactions to their national agency

5. FDA submission dossier. Auxilium Pharmaceuticals 2009.

Please see the Summary of product characteristics for full information.

Further information is available on request from: medical.info@sobi.com, Tel:+46(8) 697 20 00.

Adverse events should be reported via the national reporting system and to Sobi at drugsafey@sobi.com.

Xiapex 0.9mg powder and solution for injection, EU/1/11/671/001.

XIAPEX®

collagenase clostridium histolyticum

sobi

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