



HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

29 February 2012

XIAPEX 0.9 mg, powder and solvent for solution for injection
B/1 vial (CIP code: 416 892.0)

Applicant: PFIZER

Collagenase Clostridium histolyticum
ATC code: M09AB02

List I

Prescription restricted to specialists in and departments of:

- orthopaedic trauma surgery
- rheumatology
- plastic, reconstructive and aesthetic surgery

Date of Marketing Authorisation (centralised procedure): 28 February 2011

Reason for request: Inclusion in the list of medicines refundable by National Health Insurance and approved for hospital use.

Medical, Economic and Public Health Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Collagenase Clostridium histolyticum

XIAPEX is a lyophilised powder containing, in a mass ratio of about 1:1, 2 collagenase enzymes: a class I collagenase (AUX-I) and a class II collagenase (AUX-II).

1.2. Background

XIAPEX is the first medicinal treatment for Dupuytren's contracture.

1.3. Indication

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

1.4. Dosage

"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.

The recommended dose of XIAPEX® is 0.58 mg per injection into a palpable Dupuytren's cord. The volume of reconstituted XIAPEX® to be administered into the Dupuytren's cord differs depending on the type of joint being treated.

Approximately 24 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. Only one cord must be treated at a time. If the disease has resulted in multiple contractures, treatment of each cord must be undertaken in a sequential order, as determined by the physician. Clinical study experience with XIAPEX® is currently limited to up to 3 injections per cord and up to 8 injections in total.

Patients should be instructed to return to see their physician the next day for an examination of the injected hand and a finger extension procedure to disrupt the cord if necessary.

Elderly

Due to the lack of quantifiable systemic exposure of XIAPEX® no dosage adjustment is necessary. No overall differences in tolerance or efficacy were observed between elderly and younger patients.

Hepatic impairment

Due to the lack of quantifiable systemic exposure, no dosage adjustment is necessary.

Renal impairment

Due to the lack of quantifiable systemic exposure, no dosage 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."

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2011)

M	: Musculo-skeletal system
M09	: Other drugs for disorders of the musculo-skeletal system
M09A	: Other drugs for disorders of the musculo-skeletal system
M09AB	: Enzymes
M09AB02	: Collagenase Clostridium histolyticum

2.2. Medicines in the same therapeutic category

There are no medicines in the same therapeutic category.

2.3. Medicines with a similar therapeutic aim

There are no medicines with a similar therapeutic aim.

The treatment of Dupuytren's contracture is mainly surgical. Among the different techniques used, the Transparency Committee believed that percutaneous needle fasciotomy was the most relevant comparator given that it necessitates a medical procedure closely related to that of XIAPEX injection and that it takes place at the same stage in therapeutic use.

3 ANALYSIS OF AVAILABLE DATA

3.1. Efficacy

The assessment of the efficacy of XIAPEX is based on 5 phase III studies:

- 3 double-blind studies versus placebo, CORD I, CORD II and DUPY-303,
- open study AUX-CC-854,
- follow-up study AUC-CC-860.

XIAPEX was not compared with needle fasciotomy (regarded by the Committee as the most relevant comparator), or with surgery.

3.1.1. Studies versus placebo

The three phase III clinical studies, CORD I, CORD II and DUPY-303, assessed the efficacy and tolerance of the XIAPEX collagenase versus placebo in the treatment of Dupuytren's contracture. Their methodologies, inclusion criteria and primary efficacy endpoint are identical.

Method: randomised, double-blind phase III study comparing XIAPEX with placebo for 90 days, stratified by the type of joint affected by the Dupuytren's cord: metacarpophalangeal (MP) or proximal interphalangeal (PIP) and the severity of the contracture: \leq or $>50^\circ$ for the MP and \leq or $>40^\circ$ for PIPs.

For each patient, one main joint with palpable cord was chosen by the investigator. This could be an MP or a PIP. Each cord could receive up to 3 injections, with 2 injections 30 days apart. Each patient was reviewed 24 h after each injection so that, if necessary, a manual extension procedure could be performed to disrupt the cord. When the treatment of the cord affecting the main joint was successful (reduction of the contracture to $\leq 5^\circ$ 30 days after the injection), one or even two cords affecting other joints could in turn be treated.

Inclusion criteria:

Patients more than 18 years of age who have Dupuytren's contracture with:

- contracture of the fingers with a palpable cord in at least one of the fingers (other than the thumb), of 20 to 100° for the MP joints and 20 to 80° for the PIP joints in the CORD I and CORD II studies. For the DUPY-303 study, the flexion had to be 20° or more,
- a palpable cord,
- a positive table top test: inability to simultaneously place the fingers and palm of the hand flat against a table top.

Primary efficacy endpoint: percentage of patients achieving clinical success, i.e. a reduction of the contracture to 5° or less for the main joint 30 days after the last injection.

Secondary endpoints:

CORD I	CORD II	DUPY-303
clinical improvement: reduction of $\geq 50\%$ in the baseline degree of contracture 30 days after the last injection.	clinical improvement: reduction of $\geq 50\%$ in the baseline degree of contracture 30 days after the last injection.	mean change in the degree of contracture in %, 30 days after the last injection
mean change in the degree of contracture in %, 30 days after the last injection	mean change in the degree of contracture in %, 30 days after the last injection	change in the amplitude of movement 30 days after the last injection
change in the amplitude of movement, 30 days after the last injection	change in the amplitude of movement, 30 days after the last injection	time needed to achieve clinical success
time needed to achieve clinical success	time needed to achieve clinical success	

Centres:

- CORD I: 16 centres in the USA,
- CORD II: 5 centres in Australia,
- DUPY-303: 1 centre in the USA.

Results:

3.1.1.1. CORD I study (AUX-CC-857)

The demographic and clinical characteristics, medical history and risk factors of the patients are presented below for the intention to treat (ITT) population, n = 308.

Characteristics, medical history and risk factors of the patients, ITT population			
	Xiapex n=204	Placebo n=104	Total n=308
Age (years), mean (SD)	62.3 (9.7)	63.3 (9.1)	62.7 (9.5)
Gender, n (%)			
Male	171 (83.8)	74 (71.2)	245 (79.5)
Total contracture index (°) ^a , mean (SD)	149.1 (127.6)	149.3 (111.4)	149.1 (122.2)
Hand with ≥ 1 contracture ^b , n (%)			
Left	54 (26.5)	28 (26.9)	82 (26.6)
Right	69 (33.8)	40 (38.5)	109 (35.4)
Both	81 (39.7)	36 (34.6)	117 (38.0)
Mean number of joints with contractures per patient, mean (SD)	3.0 (2.2)	3.0 (2.1)	3.0 (2.2)
Family history of Dupuytren's contracture, n (%)			
Yes	85 (41.7)	53 (51.0)	138 (44.8)

Characteristics, medical history and risk factors of the patients, ITT population			
	Xiapex n=204	Placebo n=104	Total n=308
History of exposure to vibration, n (%)			
Yes	26 (12.7)	11 (10.6)	37 (12.0)
History of hand injury, n (%)			
Yes	56 (27.5)	21 (20.2)	77 (25.0)
History, n (%)			
Dorsal knuckle pads	9 (4.4)	7 (6.7)	16 (5.2)
Peyronie disease	10 (4.9)	6 (5.8)	16 (5.2)
Ledderhose disease	14 (6.9)	8 (7.7)	22 (7.1)
Diabetes	13 (6.4)	7 (6.7)	20 (6.5)
Epilepsy	4 (2.0)	3 (2.9)	7 (2.3)
Alcohol consumption, n (%)			
Yes	167 (81.9)	80 (76.9)	247 (80.2)
Previous treatment of Dupuytren's contracture, n (%)			
None	125 (61.3)	54 (51.9)	179 (58.1)
Surgery	73 (35.8)	44 (42.3)	117 (38.0)
Physiotherapy	28 (13.7)	16 (15.4)	44 (14.3)
Injection	5 (2.5)	3 (2.9)	8 (2.6)
Other	8 (3.9)	4 (3.8)	12 (3.9)
<small>^a: sum of all degrees of contracture of $\geq 20^\circ$ caused by a Dupuytren's cord for the 16 joints assessed before treatment; ^b: number of joints, before treatment, with a contracture of $\geq 20^\circ$ due to a Dupuytren's cord.</small>			

The mITT (modified intention to treat) analysis covered 306 patients, 203 in the XIAPEX group and 103 in the placebo group. The mITT population was the ITT population minus the patients for whom no measurement at 30 days after the first injection was available or those whose initial contracture was between 0 and 5° on selection and one day after treatment (n = 1 in each group).

The clinical success rate in the XIAPEX group, 64% (130/203), was significantly greater than that in the placebo group, 6.8% (7/103), $p < 0.001$.

The clinical success rate was:

- 76.7% for cords affecting the MP joints and 40% for the PIPs,
- 88.9% for cords causing mild contracture of the MP ($\leq 50^\circ$) and 57.7% for cords causing severe contracture of the MP ($> 50^\circ$),
- 80.9% for cords causing mild contracture of the PIP ($\leq 40^\circ$) and 22.4% for cords causing severe contracture of the PIP ($> 40^\circ$),

The mean number of injections administered to achieve clinical success was 1.7 for the XIAPEX group and 2.9 for the placebo group.

The results for XIAPEX versus placebo for the 4 secondary endpoints regarding treatment of the cord affecting the main joint are presented below:

- clinical improvement: 172/203 (84.7%) versus 12/103 (11.7%), $p < 0.001$,
- mean change in the degree of contracture in %, 30 days after the last injection: 79.3% versus 8.6%, $p < 0.001$,
- change in the amplitude of movement, 30 days after the last injection: 36.7° versus 4°, $p < 0.001$,
- time needed to achieve clinical success: median of 56 days for the XIAPEX group and not calculable for the placebo group.

3.1.1.2. CORD II study (AUX-CC-859)

The ITT analysis covered 66 patients, 45 in the XIAPEX group and 21 in the placebo group. The demographic and clinical characteristics, medical history and risk factors of these patients are presented below.

Characteristics, medical history and risk factors of the patients, ITT population			
	Xiapex (n=45)	Placebo (n = 21)	Total (n=66)
Age (years), mean (SD)	63.0 (7.8)	65.5 (11.1)	63.8 (9.0)
Gender, n (%)			
Male	39 (86.7)	17 (81.0)	56 (84.8)
Total contracture index ^a			
Mean (SD)	174.7 (107.2)	150.1 (84.0)	166.9 (100.4)
Hand with ≥ 1 contracture ^b , n (%)			
Left	12 (26.7)	5 (23.8)	17 (25.8)
Right	11 (24.4)	4 (19.0)	15 (22.7)
Both	22 (48.9)	12 (57.1)	34 (51.5)
Mean number of joints affected ^b per patient			
Mean (SD)	3.4 (2.3)	3.0 (1.5)	3.3 (2.1)
Family history of Dupuytren's contracture, n (%)			
Yes	22 (48.9)	9 (42.9)	31 (47.0)
History of exposure to vibration, n (%)			
Yes	13 (28.9)	6 (28.6)	19 (28.8)
History of hand injury, n (%), Yes	12 (26.7)	4 (19.0)	16 (24.2)
History, n (%)			
Dorsal knuckle pads	0	0	0
Peyronie disease	1 (2.2)	1 (4.8)	2 (3.0)
Ledderhose disease	0	0	0
Diabetes	6 (13.3)	0	6 (9.1)
Epilepsy	2 (4.4)	0	2 (3.0)
Alcohol consumption, Yes	43 (95.6)	19 (90.5)	62 (93.9)
Previous treatment of Dupuytren's contracture, n (%)			
None	21 (46.7)	10 (47.6)	31 (47.0)
Surgery	24 (53.3)	11 (52.4)	35 (53.0)
Physiotherapy	4 (8.9)	1 (4.8)	5 (7.6)
Injection	0	0	0
Other	0	0	0

^a: sum of degrees of contracture of $\geq 20^\circ$ caused by a Dupuytren's cord for the 16 joints assessed before treatment;
^b: number of joints with a contracture of $\geq 20^\circ$ due to a Dupuytren's cord before treatment.

There was more clinical success in the XIAPEX group (20/45) than in the placebo group (1/21, $p < 0.001$).

The mean number of injections administered to achieve clinical success for the main joint was 1.7 for the XIAPEX group and 2.8 for the placebo group.

After the last injection, clinical success was:

- 13/20 for cords affecting the MP joints and 7/25 for the PIPs.
- 7/10 for cords causing mild contracture of the MP ($\leq 50^\circ$) and 6/10 for cords causing severe contracture of the MP ($> 50^\circ$),
- 2/5 for cords causing mild contracture of the PIP ($\leq 40^\circ$) and 5/20 for cords causing severe contracture of the PIP ($> 40^\circ$),

The results for XIAPEX versus placebo for the 4 secondary endpoints regarding treatment of the cord affecting the main joint are presented below:

- clinical improvement: 35/45 versus 3/21, $p < 0.001$
- mean change in the degree of contracture in %, 30 days after the last injection: 70.5% versus 13.6%, $p < 0.001$,
- change in the amplitude of movement, 30 days after the last injection: 35.4° versus 7.6° , $p < 0.001$,
- time needed to achieve clinical success: median of 57 days for the XIAPEX group versus not calculable for the placebo group.

Among patients in whom clinical success was not achieved, 25% of MPs and 48% of PIPs had not received the 3 injections scheduled in the protocol.

3.1.1.3. DUPY-303 study

The ITT analysis covered 35 patients, 23 in the XIAPEX group and 12 in the placebo group. The scheduled number of subjects needed was 116 patients, i.e. 68 cords affecting a main MP joint and 48 a PIP.

The demographic and clinical characteristics, medical history and risk factors of these patients are presented below.

Characteristics, medical history and risk factors of the patients – ITT population			
	Xiapex (n = 23)	Placebo (n=12)	Total (n=35)
Age (years)			
Mean (SD)	60.1 (7.6)	63.8 (10.0)	61.3 (8.5)
Gender, n (%)			
Male	20 (87.0)	8 (66.7)	28 (80.0)
History, n (%)			
Family history of Dupuytren's contracture	11 (47.8)	6 (50.0)	17 (48.6)
Hand injury	4 (17.4)	1 (8.3)	5 (14.3)
Dorsal knuckle pads	6 (26.1)	2 (16.7)	8 (22.9)
Peyronie disease	4 (17.4)	0	4 (11.4)
Ledderhose disease	7 (30.4)	2 (16.7)	9 (25.7)
Diabetes	3 (13.0)	0	3 (8.6)
Previous treatments of Dupuytren's contracture, n (%)			
Surgery	10 (43.5)	5 (41.7)	15 (42.9)
Physiotherapy	4 (17.4)	3 (25.0)	7 (20.0)
Steroid injection	1 (4.3)	0	1 (2.9)
Other	2 (8.7)	3 (25.0)	5 (14.3)
Degree of contracture (in °)			
Mean (SD)	52.0 (13.38)	43.8 (10.90) ^b	-
^a : the p values correspond to an analysis of variance with treatment as factor			
^b : p=0.077			

There was more clinical success in the XIAPEX group (21/23) than in the placebo group (0/12, $p < 0.001$).

The mean number of injections to achieve success was 1.3 in the XIAPEX group and not applicable in the placebo group.

Clinical success was 12/14 for cords affecting the MP joints and 0/7 for the PIPs.

The results for XIAPEX versus placebo for the 3 secondary endpoints regarding treatment of the cord affecting the main joint are presented below:

- mean change in the degree of contracture in %, 30 days after the last injection (95.6% versus 0, $p < 0.001$);
- change in the amplitude of movement, 30 days after the last injection (150.4% versus 4.2%, $p < 0.001$);
- time needed to achieve clinical success: median of 8 days versus not calculable for the placebo group.

3.1.2. Open study AUX-CC-854

Method: non-comparative phase III study assessing the efficacy and tolerance of XIAPEX for 9 months. There was no choice of main joint. Each Dupuytren's cord could receive up to 3 injections, 2 injections 30 days apart, with a maximum of 5 injections per patient. This study was conducted at 20 centres in Australia and Europe.

Inclusion criteria: patient ≥ 18 years of age with a diagnosis of Dupuytren's contracture with a contracture (20 to 100° for the MPs and 20 to 80° for the PIPs), a palpable cord and a positive table top test.

Primary efficacy endpoint: percentage of patients achieving clinical success, i.e. a reduction of the contracture to 5° or less for the main joint 30 days after the last injection.

Secondary endpoints:

- clinical improvement: reduction of $\geq 50\%$ in the baseline degree of contracture 30 days after the last injection,
- mean change in the degree of contracture in %, 30 days after the last injection,
- change in the amplitude of movement 30 days after the last injection
- time needed to achieve clinical success.

Results: The ITT analysis covered 386 patients, of whom 137 were European.

The clinical success rate with XIAPEX was 58.4% (50.5% for the European patients) for a total of 587 cords treated (214 in Europe). The mean number of injections needed for success was 1.2.

Clinical success was more frequent for cords affecting the MP joints, at 243/343 (70.8%) compared with the PIPs with 100/244 (41%).

The results for the 4 secondary endpoints regarding treatment of the cord affecting the main joint are presented below:

- clinical improvement: 463/587 (78.9%)
- mean change in the degree of contracture in %, 30 days after the last injection 75.4%
- mean change in the amplitude of movement, 30 days after the last injection: 30.7°
- time needed to achieve clinical success: 48.4% of cords treated showed clinical success less than 30 days after the first injection

Eight recurrences (contracture of $\geq 20^\circ$ and palpable cord), of which 5 on a PIP were observed among the cords treated successfully (n = 343), i.e. 2.3% in 9 months.

3.1.3. Follow-up study AUX-CC-860 (interim report at 2 years)

Method: open phase III study assessing the efficacy, tolerance and recurrence rate after treatment of Dupuytren's contracture with XIAPEX over 5 years. The centres are located in the USA, in Australia and in Europe.

Inclusion criteria: patient having received at least 1 injection of XIAPEX in one of the following studies, AUX-CC-854, AUX-CC-856 (non-comparative phase III study), CORD I, AUX-CC-858 (open extension of CORD I) and CORD II, and with at least one measurement of contracture after treatment.

Primary efficacy endpoint: recurrence rate, recurrence being defined as measurement of a contracture of $\geq 20^\circ$ with palpable cord in a patient who was previously treated successfully with XIAPEX.

Results: the analysis covered 634 patients representing 1065 treated cords, of whom 619 (449 MP + 170 PIP) showed clinical success in the previous study.

The recurrence rate at 1 year was 3.1%.

The nominal cumulative recurrence rate at 2 years was 19.3% for all successfully treated cords (119/618), including 13.6% for those affecting the MP joints (61/448) and 34.1% for the PIPs (58/170). The recurrence rate at 2 years estimated by the Kaplan-Meier method was 24.1%.

The nominal cumulative recurrence rate at 3 years was 34.8% for all successfully treated cords (217/623), including 26.6% for those affecting the MP joints (120/451) and 56.4% for the PIPs (97/172).

3.2. Adverse effects

3.2.1. Adverse effects in clinical studies

3.2.1.1. CORD I study

In the ITT population, during the 90 days of treatment, 97.1% (198/204) of patients had an adverse event in the XIAPEX group and 47.1% (49/104) in the placebo group, of which percentages 96.6% (197/204) and 21.2% (22/104) were linked to the treatment.

The most common adverse events were as follows (XIAPEX versus placebo):

- peripheral oedema: 72.5% vs. 3.8%
- contusion: 51% vs. 1.9%,
- haemorrhage at the injection site: 37.3% vs. 3.8%,
- pain at the injection site: 32.4% vs. 4.8%,
- pain in the extremities: 30.9% vs. 2.9%.

Most of these adverse effects appeared on the day of the injection or the manipulation. No increase in the duration or intensity of the adverse effects with the number of injections was observed.

Adverse events that were severe and “probably” linked to the treatment occurred in 20/204 (9.8%) patients in the XIAPEX group versus 2/104 (1.9%) in the placebo group. The commonest ones were as follows:

- peripheral oedema: 2% vs 0,
- pain at the injection site: 2% vs 0,
- pain in the extremities: 2% vs 0,
- haemorrhage at the injection site: 1.5% vs 0,
- contusion: 1% vs 0.

Three serious adverse effects were described (3/204; 1.5%): 2 ruptures of the tendon treated and 1 complex regional pain syndrome (algodystrophy).

More than 80% of patients developed antibodies to collagenases AUX-I and AUX-II 30 days after the first injection of XIAPEX without any serious systemic immunoallergic adverse event occurring.

3.2.1.2. CORD II study

In the ITT population, during the 90 days, 100% (45/45) of patients had an adverse event in the XIAPEX group and 57.1% (12/21) in the placebo group, of which percentages 100% (45/45) and 38.1% (8/21) were linked to the treatment.

The most common adverse effects were as follows (XIAPEX versus placebo):

- peripheral oedema: 77.8% vs. 9.5%,
- contusion: 73.3% vs. 9.5%,
- pain in the extremities: 48.9% vs. 9.5%,
- haemorrhage at the injection site: 42.2% vs 0,
- pain at the injection site: 37.8% vs. 9.5%.

Most of these adverse effects appeared on the day of the injection or the manipulation. No increase in the duration or intensity of the adverse effects with the number of injections was observed.

Five severe adverse events were described with a probable link to treatment: ligament injury (n=1), pain at the injection site (n=1), pain in the extremities (n=2) and contusion (n=1).

One serious adverse event which was probably linked to the treatment was reported among the 45 patients treated with XIAPEX (2.2%). This was pulley rupture on flexion of the left little finger. A pulley is a local reinforcement of the sheath of the flexor tendons which holds the tendon against the bone.

About 90% of patients developed antibodies to collagenases AUX-I and AUX-II 30 days after the first injection of XIAPEX without any serious systemic immunoallergic adverse event occurring.

3.2.1.3. DUPY-303 study

In the ITT population, during the 90 days of treatment, 100% (23/23) of patients had an adverse event in the XIAPEX group and 80% (12/15) in the placebo group.

The most common adverse events were as follows (XIAPEX versus placebo):

- peripheral oedema: 100% vs. 6.7%
- pain at the injection site: 100% vs. 46.7%
- contusion: 52.2% vs 0.
- haemorrhagic phlyctena: 43.5% vs 0.
- lymphadenopathy: 43.5% vs 0.

Most of the adverse effects appeared on the day of the injection or the manipulation and did not increase in duration or intensity with the second or third injection.

No serious adverse event linked to treatment was reported.

3.2.1.4. AUX-CC-854 study

In the ITT population, 97.9% (378/386) of patients had an adverse event after injection of XIAPEX, of which a figure of 97.7% (377/386) was linked to the treatment.

The adverse effects reported most frequently were as follows:

- peripheral oedema: 75.4%
- contusion: 64.8%
- pain in the extremities: 46.6%
- pain at the injection site: 34.7%
- haemorrhage at the injection site: 29%

Most of these adverse effects appeared on the day of the injection or the manipulation. No increase in the duration or intensity of the adverse effects with the number of injections was observed.

Among the 39 patients who presented at least one serious adverse event, one case of tendinitis was probably linked to the treatment (1/386; 0.3%).

One death from myocardial infarction occurred during the study but was not linked to the treatment.

About 90% of patients developed antibodies to collagenases AUX-I and AUX-II 30 days after the first injection of XIAPEX without any serious systemic immunoallergic adverse event occurring.

3.2.1.5. AUX-CC-860 study

Among the 643 patients followed up for 3 years in this study, 193 had an adverse event, i.e. 30%. Most of them were mild or moderate. None were linked to the treatment. Three patients (0.5%) died during follow-up; these deaths were not linked to the treatment.

The concentrations of antibodies to AUX-I and AUX-II increased with the number of injections of XIAPEX, with a plateau after the fourth injection, then progressively decreased or stabilised. In patients who received a single injection of XIAPEX, the concentration of antibodies to collagenase went from 98.1% in the first positive analysis to 82.6% in the second year of follow-up then 81.2% in the third year.

In those who received two injections, the concentration of antibodies to collagenase went from 99.2% in the first positive analysis to 96% in the second year of follow-up then 98.2% in the third year.

For patients who received more than 2 injections, the percentage of antibodies remained constant during follow-up (100%).¹

3.2.2. Pharmacovigilance data

The available pharmacovigilance data (4 PSURs) covering the period from 02 February 2010 to 02 February 2011 did not show any particular signal.

A European risk management plan (RMP) was set up. It concerns the proven or potential risks of treatment with XIAPEX. The proven risks are: local immune reactions, skin lesions, rupture of or damage to the tendon or ligament. The potential risks are: bleeding at the injection site in patients with coagulation disorders or in those who are receiving an anticoagulant, cross-reactions with endogenous metalloproteinases, drug errors, anaphylaxis and systemic hypersensitivity. The RMP comprises:

- The pharmacovigilance plan with routine pharmacovigilance and a 5-year follow-up study. The AUX-CC-860 study is currently in progress and its aim is to assess the rate of recurrence, progression of the disease on cords that were untreated or were not treated successfully, and long-term tolerance. Another study was requested in order to assess the inhibition of human proteins by neutralising antibodies to collagenases AUX I and AUX II in patients who received several injections of XIAPEX.
- The risk minimisation plan with the training of doctors authorised to use XIAPEX and 3 other clinical studies. The B1531003 study will compare the efficacy of XIAPEX, fasciectomy and fasciotomy over 5 years. The AUX-CC-862 and AUX-CC-863 studies will assess the efficacy and tolerance of XIAPEX in the treatment of recurrences of Dupuytren's contracture after a first treatment with XIAPEX.

3.3. **Conclusion**

The assessment of XIAPEX in patients with Dupuytren's contracture is based mainly on 5 studies, 3 of which were double-blind versus placebo and 2 non-comparative.

The 3 studies CORD I, CORD II and DUPY-303, which were randomised, double-blind versus placebo, showed the superiority of XIAPEX by comparison with placebo as regards the success rate in the treatment of the cord affecting the main joint (primary efficacy endpoint). These rates were 64% with XIAPEX vs 6.8% with placebo in the CORD I study, 20/45 vs 1/21 in CORD II and 21/23 vs 0/12 in DUPY-303.

In the main studies, CORD I and II, most of the patients included (72%) had a stage I or II Tubiana score (corresponding to stages that are not very advanced): 46 patients had a Tubiana I score (overall contracture between 0° and 45°), 64 a score of II (overall contracture between 45° and 90°), 29 a score of III (overall contracture between 90° and 135°) and 14 a score of IV (overall contracture of more than 135°). Conditions involving the thumb were not included in these studies.

XIAPEX was not compared with the treatments usually used in the management of Dupuytren's contracture (needle fasciotomy and surgery).

Among the 2 non-comparative studies, one (AUX-CC-854) included centres in Europe and had a success rate after 9 months' treatment of 58.4% for all the patients included and 50.5% for European patients. The other study (AUX-CC-860), which is still ongoing, is assessing, over 5 years, the recurrence of the disease after treatment with XIAPEX in patients previously included in one of the 5 phase III studies. The interim analysis shows a recurrence rate of 3.1% at 1 year, 19.3% at 2 years for all cords treated successfully, including 13.6% for cords affecting the MP joints (61/448) and 34.1% for the PIPs (58/170) and 34.8% at 3 years for all cords treated successfully (217/623) including 26.6% for those affecting the MP joints (120/451) and 56.4% for the PIPs (97/172).

¹ Source pharmaceutical company's internal study report

Between 97% and 100% of patients who received at least one injection of XIAPEX had an adverse effect. These effects, which were in most cases local, mild or moderate, were: peripheral oedema, contusion, haemorrhage at the injection site, pain at the injection site and pain in the extremities. The following serious adverse effects were also observed: 3 tendon ruptures, 1 pulley rupture, 1 tendinitis and 1 complex pain syndrome.

Most patients developed antibodies to collagenases AUX-I and AUX-II within 30 days after the first injection. No serious systemic immunoallergic reaction was observed in these studies, but local immunoallergic reactions (pruritus, lymph node pain, lymphadenopathy, erythema, axillary pain, pruritus at the injection site, peripheral oedema) were described in 5 to 45% of patients. Although the follow-up data at 3 years did not reveal any clinical manifestation linked to the presence of antibodies to collagenase after the injection of XIAPEX, the immunological consequences must be studied in the longer term, particularly in patients who received 2 or more injections of XIAPEX.

Overall, XIAPEX, a medical treatment for Dupuytren's contracture, is superior to placebo for patients with a contracture and a palpable cord, but it was not compared with the usual treatments, needle fasciotomy and surgery. The recurrence rate was assessed as 19.3% at 2 years and 34.8% at 3 years (including 56.4% for PIP joints) in a single study and its longer-term course is unknown.

Needle fasciotomy, a minimally invasive technique the implementation of which is closely related to that of the injection of XIAPEX, is regarded by the Committee as being the most relevant comparator.

In view of the heterogeneity of the criteria used to define recurrence in the published studies which assessed the efficacy of the different techniques for managing Dupuytren's contracture, it is difficult to make a direct comparison. By way of information, it is estimated that the recurrence rate after needle fasciotomy is 60% at 3 years², and 50% at 5 years.³

² S M Crean et al. The efficacy and safety of fasciectomy and fasciotomy for Dupuytren's contracture in European patients: a structured review of published studies. *J Hand Surg Eur.* Vol 7 march 2011.

³ Badois FJ, Lermusiaux JL, Massé C, Kuntz D. Non-surgical treatment of Dupuytren disease using needle fasciotomy. *Rev Rhum Ed Fr.* 1993 Nov 30;60(11):808-13.

4 ADDITIONAL DATA

XIAPEX is currently refundable by health insurance in Germany pending the final opinion of the Federal [Joint] Committee following the IQWIG assessment of 1 February 2012, in the United Kingdom, Spain, Austria, Ireland, Denmark, Finland, Norway and Sweden.

NICE assessments regarding Dupuytren's contracture:

NICE, in its assessment report of 2004⁴, on the basis of the available tolerance and efficacy data, believed that needle fasciotomy was a validated technique in the management of Dupuytren's contracture. The recurrence rate was about 50% at 3-5 years and seemed to be dependent on the severity of the condition. Some data suggested that patients with a less severe condition and/or an affected metacarpophalangeal joint benefitted more from this technique.

No assessment of XIAPEX by NICE is available.

Assessment by IQWIG

The IQWIG concluded that no added benefit had been demonstrated for XIAPEX in Dupuytren's contracture. This conclusion was justified by the lack of relevant data in the dossier supplied by Pfizer, and particularly the absence of comparative data on the therapies chosen by the Federal Joint Committee (GBA) representing medical associations, health insurance funds and hospitals.

The IQWIG felt that the appropriate comparator for XIAPEX differed according to the severity of the condition affecting the function of the fingers and hand.

Thus, the following alternative treatment strategies were considered according to the stage of the condition (defined according to the Tubiana classification which measures overall retraction of the fingers):

- in the absence of contracture (stage 0), the alternative considered was "no treatment"
- for stages I (total contracture between 0° and 45°) and II (total contracture between 45° and 90°), needle fasciotomy was the comparison treatment
- for stages III (total contracture between 90° and 135°) and IV (total contracture of more than 135°), the comparison was surgical, partial fasciectomy; if partial fasciectomy was contraindicated, needle fasciotomy could be considered as the comparison treatment.

For elderly patients, when the surgical option cannot be considered, needle fasciotomy can be used.

The company's decision to regard the surgical technique "partial fasciectomy" as the sole comparator for XIAPEX in its dossier was regarded as being insufficiently justified. In all cases, no study comparing XIAPEX with the different alternatives was included in the dossier. Just one indirect comparison, which was considered unacceptable, was supplied.

The final decision will be given in April-May 2012.

⁴ NICE. Needle fasciotomy for Dupuytren's contracture - February 2004.

National Insurance reimbursement data relating to needle fasciotomy and surgical procedures in Dupuytren's contracture (2010)

	Private practice	External consultations in a public hospital	Homogeneous patient groups (HPG) (hospitalisation in a public hospital)	HPG (hospitalisation in a private hospital)	TOTAL
Needle fasciotomy = code MJPB 001 Fasciotomy, palmar, transcutaneous aponeurotomy	3422	2228	438	527	6615
Surgery = code MJFA 006 Palmodigital fasciotomy (aponeurotomy) on one digital ray, direct approach	244	9	2062	6194	8509
Surgery = code MJFA 010 Palmodigital fasciotomy (aponeurotomy) on several digital rays, direct approach	125	5	1862	6128	8120
Surgery = code MJPA 005 Palmar fasciotomy (aponeurotomy), direct approach	104	16	483	1057	1660

Needle fasciotomy procedures account for 26.6% of procedures in the management of Dupuytren's disease, and surgery 73.4%.

5 TRANSPARENCY COMMITTEE CONCLUSIONS

5.1. Actual benefit

Dupuytren's contracture is a disease which, when fully developed, can lead to substantial functional disability of the hand.

This proprietary medicinal product is intended as symptomatic treatment.

Adverse effects after treatment with XIAPEX are very common. Most are not severe, but serious adverse effects have occurred: tendon ruptures, pulley rupture, tendinitis and complex pain syndrome.

The long-term recurrence rate is uncertain: it was 3% at 1 year and 19.3% at 2 years and 34.8% at 3 years in the sole follow-up study currently in progress. There is also uncertainty about long-term safety, particularly because of the appearance, almost invariably after 2 injections, of antibodies to collagenase. Consequently, the efficacy/tolerance ratio of this medicinal product in this indication cannot be stated.

Public health benefit:

Dupuytren's contracture is a common, often irreversible, progressive and bilateral disease which can lead to substantial functional disability of the hand. The prevalence of this disease varies, according to the populations studied and the data collection methods used, between 0.2% and 56%.⁵ The burden of all musculo-skeletal disorders, which includes numerous diseases, can be regarded as substantial (about 300,000 DALYs); that of the indication for XIAPEX, Dupuytren's contracture in adult patients with a palpable cord, can be regarded as low.

Management of Dupuytren's contracture is not a public health need.

In view of the available data versus placebo, a low impact of XIAPEX on morbidity can be expected. However, the transferability of the results of clinical studies is debatable, particularly in view of the potential long-term immunological consequences associated with the virtually inevitable development of antibodies to collagenases AUX-I and AUX-II in treated patients, the absence of comparative data versus needle fasciotomy and other surgical treatments and the absence of data on the frequency of medium- and long-term recurrences.

Given, in particular, the not inconsiderable recurrence rate, the inability to treat several cords simultaneously and the need for a consultation the day after treatment, XIAPEX could have a negative impact on the organisation of the healthcare system.

Consequently, it is not anticipated that XIAPEX will benefit public health in the treatment of Dupuytren's contracture.

There are treatment alternatives with which XIAPEX has not been compared: needle fasciotomy, multiaponeurotomy (simultaneous treatment of several cords), limited fasciectomy, dermofasciectomy and total fasciectomy.

In France, the needle fasciotomy technique is well established. It is carried out by orthopaedic and rheumatology surgeons trained in this technique. It allows the simultaneous treatment of several Dupuytren's cords on an outpatient basis (in the operating theatre or in general practice) with immediate resumption of activities and no consultation 24 h after the procedure. Complications are rare and always minor.

It is not possible to treat several Dupuytren's cords with XIAPEX simultaneously since 2 injections must be given 4 weeks apart with a maximum of 3 injections per cord and 8 per

⁵ Hindocha S et al. Epidemiological evaluation of Dupuytren's disease incidence and prevalence rates in relation to etiology. Hand (N Y) 2009;4: 256-269.

patient. Treatment with XIAPEX necessitates an additional consultation after 24 h so that an extension manoeuvre can be carried out if necessary. In addition, unlike needle fasciotomy, follow-up in terms of tolerance and recurrence is limited to 3 years for XIAPEX.

Overall, in the absence of any comparison of XIAPEX with needle fasciotomy (the most relevant comparator in France) or surgery, it is not possible to determine the place of this medicinal product in the strategy for the management of Dupuytren's contracture.

In view of:

- the absence of any comparison of XIAPEX with a relevant technique (needle fasciotomy, surgery);
- the high percentage of adverse effects;
- the uncertainty about its long-term safety associated with the virtually inevitable appearance, after 2 injections, of antibodies to collagenase;
- the continuing uncertainty about the long-term recurrence rate;
- the possible negative impact of XIAPEX on the organisation of the healthcare system (administration protocol);

the Transparency Committee considers that, given the current state of the dossier, the actual benefit of this proprietary medicinal product **is insufficient**, in view of the treatments available, to justify its reimbursement by National Insurance.

The Committee wishes to reassess this product in the light of any new data that can be supplied to it.

5.2. Transparency Committee recommendations

The transparency Committee does not recommend inclusion on the list of medicines refundable by National Health Insurance or on the list of medicines approved for hospital use and various public services in the indications and at the dosages given in the Marketing Authorisation.