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WHAT TO EXPECT AFTER YOUR EUFLEXXA INJECTIONS

Please see Important Safety Information on back cover and Full Prescribing Information in pocket.

What should I do after receiving a EUFLEXXA injection?

- Avoid physical activity for 48 hours after receiving your EUFLEXXA injection to keep your knee from swelling
- Ice your knee if you have any mild pain or swelling near the injection site
- Avoid standing on your feet for more than 1 hour at a time during the first 48 hours following the injection
- Ask your healthcare provider when you should begin major physical activities again
- Call your doctor immediately if you experience joint pain, back pain, limb/muscle pain, joint swelling, or any other problems

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What should I expect from treatment with EUFLEXXA?

- Some people experience moderate pain relief after the 1st or 2nd injection of EUFLEXXA.
- Most people experience significant relief after the 3rd (last) injection.
- For maximum pain relief, be sure to get **all 3 injections**.
- When it comes to duration of pain relief, each person is different. In general, 1 course of 3 EUFLEXXA injections has been shown to provide up to 6 months of knee pain relief.
- The most common adverse events related to EUFLEXXA injections were joint pain, back pain, limb pain, muscle pain, and joint swelling.

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SCHEDULE ALL 3 INJECTIONS TODAY!

1 date: time:

2 date: time:

3 date: time:

INDICATION

EUFLEXXA (1% sodium hyaluronate) is used to relieve knee pain due to osteoarthritis. It is used for patients who do not get enough relief from simple pain medications such as acetaminophen or from exercise and physical therapy.

EUFLEXXA is only for injection into the knee, performed by a doctor or other qualified healthcare professional.

IMPORTANT SAFETY INFORMATION

- Do not take this product if you have had any previous allergic reaction to EUFLEXXA or hyaluronan products.
- You should not have EUFLEXXA injected into the knee if you have a knee joint infection or skin diseases or infections around the injection site.
- EUFLEXXA has not been tested in pregnant women, women who are nursing or children less than 18 years of age. After you receive your EUFLEXXA injection you should avoid physical activities for 48 hours such as jogging, tennis, heavy lifting, or standing on your feet for a long time (more than one hour at a time).
- The most common adverse events related to EUFLEXXA injections were joint pain, back pain, limb pain, muscle pain, and joint swelling.

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FERRING PHARMACEUTICALS

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Product Code: 55566-4100-1
6309501103
Rev. 07/2016

PRODUCT INFORMATION
EUFLEXXA®
(1% sodium hyaluronate)

CONTENT
Each 1 mL of EUFLEXXA contains:

Sodium hyaluronate	10 mg
Sodium chloride	8.5 mg
Disodium hydrogen phosphate dodecahydrate	0.56 mg
Sodium dihydrogen phosphate dihydrate	0.05 mg
Water for injection	q.s.

DESCRIPTION
EUFLEXXA is a viscoelastic, sterile solution of highly purified, high molecular weight (2.4-3.6 million daltons) hyaluronan (also known as sodium hyaluronate) in phosphate-buffered saline. EUFLEXXA is a very highly purified product extracted from bacterial cells. It is a polysaccharide consisting of repeating disaccharide of N-acetylglucosamine and sodium glucuronate, linked by alternating β →1,3 and β → 1,4 glycosidic bonds.

INDICATION
EUFLEXXA (1% sodium hyaluronate) is indicated for the treatment of pain in osteoarthritis (OA) of the knee in patients who have failed to respond adequately to conservative non-pharmacologic therapy and simple analgesics (e.g., acetaminophen).

CONTRAINDICATIONS
- Do not use EUFLEXXA to treat patients who have a known hypersensitivity to hyaluronan preparations.
- Do not use EUFLEXXA to treat patients with knee joint infections, infections or skin disease in the area of the injection site.

WARNINGS
- Mixing of quaternary ammonium salts such as benzalkonium chloride with hyaluronan solutions results in formation of a precipitate.
  EUFLEXXA should not be administered through a needle previously used with medical solutions containing benzalkonium chloride. Do not use disinfectants for skin preparation that contain quaternary ammonium salts.
- Do not inject intravascularly because intravascular injection may cause systemic adverse events.

PRECAUTIONS
GENERAL
- Patients having repeated exposure to EUFLEXXA have the potential for an immune response; however, this has not been assessed in humans.
- Safety and effectiveness of injection in conjunction with other intra-articular injectables, or into joints other than the knee has not been established.
- Remove any joint effusion before injecting.
- Transient pain or swelling of the injected joint may occur after intra-articular injection with EUFLEXXA.
- Do not use after expiration date.
- Protect from light.
- Do not re-use — dispose of the syringe after use.
- Do not use if the blister package is opened or damaged.

Information for Patients
- Provide patients with a copy of the Patient Information prior to use.
- Transient pain and/or swelling of the injected joint may occur after intra-articular injection of EUFLEXXA.
- As with any invasive joint procedure, it is recommended that the patient avoid any strenuous activities or prolonged (i.e., more than 1 hour) weight-bearing activities such as jogging or tennis within 48 hours following intra-articular injection.
- The safety of repeated treatment cycles of EUFLEXXA has been established up to 1 year.

Use in Specific Populations
- **Pregnancy:** The safety and effectiveness of EUFLEXXA have not been established in pregnant women.
- **Nursing Mothers:** It is not known if EUFLEXXA is excreted in human milk. The safety and effectiveness of EUFLEXXA have not been established in lactating women.
- **Children:** The safety and effectiveness of EUFLEXXA have not been demonstrated in children.

ADVERSE REACTIONS
Adverse event information regarding the use of EUFLEXXA as a treatment for pain in OA of the knee was available from two sources; a 12 week multicenter clinical trial conducted in Germany, and a 26 week multicenter clinical trial conducted in the US.

Reported Device-Related Adverse Events
The most common adverse events related to EUFLEXXA injections reported in the clinical studies are the following:
- Arthralgia
- Back pain
- Pain in extremity
- Musculoskeletal pain
- Joint swelling

All adverse events related to EUFLEXXA injections reported in Tables 1, 2, 3 and 4.

Potential Adverse Events
The following adverse events are among those that may occur in association with intra-articular injections
- Arthralgia
- Joint swelling
- Joint effusion
- Injection site pain
- Arthritis

12 Week Multicenter Clinical Study
This clinical investigation was a prospective randomized, double-blinded, active control (commercially available hyaluronan product) study conducted at 10 centers. Three hundred twenty-one patients were randomized into groups of equal size to receive either EUFLEXXA (n=160) or the active control (n=161).

A total of 119 patients reported 196 adverse events; this number represents 54 (33.8%) of the EUFLEXXA group and 65 (44.4%) of the active control group. There were no deaths reported during the study. Incidences of each event were similar for both groups, except for knee joint effusion, which was reported by 9 patients in the active control group and one patient in the EUFLEXXA treatment group. Fifty-two adverse events were considered device-related. Table 1 lists the adverse events reported during this investigation.

Table 1. Incidence of Adverse Events Reported by >1% of Patients

Body System	ADE	Patients, n (%)	
		EUFLEXXA (n = 160)	Active Control (n = 161)
Gastrointestinal disorders	Nausea	3 (1.88)	0
General disorders and administration site	Fatigue	2 (1.25)	0
Infections and infestations	Bronchitis	1 (0.63)	2 (1.24)
	Infection	2 (1.25)	0
Investigations	Blood pressure increased	6 (3.75)	1 (0.62)
Musculoskeletal, connective tissue and bone	Arthralgia	14 (8.75)	17 (10.6)
	Arthrosis	2 (1.25)	0
	Back pain	8 (5.00)	11 (6.83)
	Joint disorder	2 (1.25)	2 (1.24)
	Joint effusion	1 (0.63)	13 (8.07)
	Joint swelling	3 (1.88)	3 (1.86)
	Pain in limb	2 (1.25)	0
	Tendonitis	3 (1.88)	2 (1.24)
Nervous system disorders	Headache	1 (0.63)	3 (1.86)
	Paresthesia	2 (1.25)	1 (0.62)
Respiratory, thoracic and mediastinal	Rhinitis	5 (3.13)	7 (4.35)
Skin and subcutaneous tissue disorders	Erythema	0	2 (1.24)
	Pruritus	0	3 (1.86)
Vascular disorders	Phlebitis	0	2 (1.24)

A total of 160 patients received 478 injections of EUFLEXXA. There were 27 reported adverse events considered to be related to EUFLEXXA injections: arthralgia – 11 (6.9%); back pain – 1 (0.63%); blood pressure increase – 3 (1.88%); joint effusion – 1 (0.63%); joint swelling – 3 (1.88%); nausea – 1 (0.63%); paresthesia – 2 (1.25%); feeling of sickness of injection – 3 (1.88%); skin irritation – 1 (0.63%); tenderness in study knee – 1 (0.63%). Four adverse events were reported for the EUFLEXXA group that the relationship to treatment was considered to be unknown: fatigue – 3 (1.88%); nausea – 1 (0.63%).

Table 2. Relationship of Adverse Effects to Treatment Groups That Were Considered to Be Treatment Related

Adverse Event	(EUFLEXXA) (Number of Reports) n = 160	Commercially Available Hyaluronan Product (Number of Reports) n = 161
Arthralgia	11	9
Back pain	1	0
Baker's cyst	0	1
Blood pressure increase	3	0
Erythema	0	1
Inflammation localized	0	1
Joint effusion	1	9
Joint swelling	3	2
Nausea	1	0
Edema lower limb	0	1
Paresthesia	2	0
Pruritus	0	1
Sickness	3	0
Skin irritation	1	0
Tenderness	1	0
TOTAL	27	25

26 Week Multicenter Study
This was a multicenter, randomized, double-blind trial evaluating the efficacy and safety of EUFLEXXA, as compared with saline, in subjects with chronic osteoarthritis of the knee followed by an open labeled safety extension study. The intervention consisted of three (3) weekly injections of study device into the target knee, with scheduled follow-up evaluations during the 26 weeks following the first injection. In the extension phase subjects received three (3) weekly injections of EUFLEXXA into the target knee with follow-up evaluation up to 52 weeks. Table 3 shows the treatment-emergent adverse events by preferred term with an incidence of ≥ 2% among treatment groups.

Table 3: Treatment-Emergent Adverse Events by Preferred Term with an Incidence of ≥ 2% among the Treatment Groups (Safety Population)

System Organ Class Preferred Term	26 Week FLEXX Study (Core)			Extension Study Repeat Injection for 52 Weeks*
	All Treatments N = 588 n (%)	Saline N = 295 n (%)	EUFLEXXA N = 293 n (%)	EUFLEXXA N = 219 n (%)
Any TEAE	326 (55.4)	169 (57.3)	157 (53.6)	96 (43.8)
Musculoskeletal and connective tissue disorders				
Arthralgia	62 (10.5)	35 (11.9)	27 (9.2)	19 (8.7)
Back pain	23 (3.9)	11 (3.7)	12 (4.1)	6 (2.7)
Pain in extremity	13 (2.2)	10 (3.4)	3 (1.0)	3 (1.4)
Musculoskeletal pain	10 (1.7)	4 (1.4)	6 (2.0)	2 (0.9)
Osteoarthritis	9 (1.5)	7 (2.4)	2 (0.7)	0
Joint swelling	8 (1.4)	4 (1.4)	4 (1.4)	6 (2.7)
Infections and infestations				
Upper respiratory tract infection	23 (3.9)	11 (3.7)	12 (4.1)	6 (2.7)
Nasopharyngitis	17 (2.9)	13 (4.4)	4 (1.4)	10 (4.6)
Sinusitis	16 (2.7)	10 (3.4)	6 (2.0)	5 (2.3)
Urinary tract infection	12 (2.0)	6 (2.0)	6 (2.0)	3 (1.4)
Injury, poisoning, and procedural complications				
Injury	17 (2.9)	9 (3.1)	8 (2.7)	9 (4.1)
Nervous system disorders				
Headache	17 (2.9)	11 (3.7)	6 (2.0)	3 (1.4)
Gastrointestinal disorders				
Diarrhea	14 (2.4)	2 (0.7)	12 (4.1)	3 (1.4)
Nausea	12 (2.0)	7 (2.4)	5 (1.7)	4 (1.8)
Respiratory, thoracic, and mediastinal disorders				
Cough	10 (1.7)	3 (1.0)	7 (2.4)	3 (1.4)
Vascular disorders				
Hypertension	18 (3.1)	5 (1.7)	13 (4.4)	1 (0.5)

*Treatment group for repeat study are for subjects who received EUFLEXXA in both the core and extension (219 out of 433).
N = number of subjects in a given treatment group for the population analyzed; n = number of subjects reporting at least one adverse event within system organ class/preferred term; (%) = percentage of subjects based on N; TEAE = treatment-emergent adverse event. Note: An adverse event was counted as a TEAE if it was either not present at baseline (prior to the first dose of double-blind study device) or present at baseline but increased in severity during the treatment period.

During the initial randomization/treatment phase, 326 (55.4%) subjects in the safety population experienced 742 TEAEs. The proportion of subjects reporting TEAEs was generally similar in the EUFLEXXA and saline groups (53.6% and 57.3%, respectively). The most common preferred term of TEAE was arthralgia (10.5% of all subjects). Thirty (5.1%) subjects experienced severe TEAEs, and the proportion with severe events was larger in the saline group (6.4%) than the EUFLEXXA group (3.8%). Overall, 10.4% of subjects had TEAEs considered related to study device, with comparable proportions in each treatment group (9.9% and 10.8% for EUFLEXXA and saline, respectively).

During the extension phase, 43.4% (188/433) of subjects reported 377 TEAEs. Of these 43.8% (96/219) subjects receiving repeated EUFLEXXA reported 199 TEAEs. The most frequently reported preferred term in subjects formerly assigned to the core study EUFLEXXA group were arthralgia (8.7%), nasopharyngitis (4.6%), injury (4.1%), upper respiratory tract infections (2.7%), joint swelling (2.7%), back pain (2.7%), and sinusitis (2.3%). Of these TEAEs 9 (4.1%) subjects had study device related AEs classified as "Certain," "Probable," "Possible" or "Un-assessable." The most common related TEAEs were arthralgia (2.3%) and joint swelling (1.4%). Table 4 shows the Study Device Related Treatment-Emergent Adverse Events by Preferred Term with an Incidence of ≥ 1 among Treatment Groups (Safety Population).

Table 4: Study Device Related Treatment-Emergent Adverse Events by Preferred Term with an Incidence of ≥ 1 among Treatment Groups (Safety Population)

System Organ Class Preferred Term	26 Week FLEXX Study (Core)			Extension Study Repeat Injection for 52 Weeks*
	All Treatments N = 588 n (%)	Saline N = 29 n (%)	EUFLEXXA N = 293 n (%)	EUFLEXXA N = 219 n (%)
Any related TEAEs	61 (10.4)	32 (10.8)	29 (9.9)	9 (4.1)
Musculoskeletal and connective tissue disorders				
Arthralgia	23 (3.9)	13 (4.4)	10 (3.4)	5 (2.3)
Joint swelling	3 (0.5)	2 (0.7)	1(0.3)	3 (1.4)
Pain in extremity	3 (0.5)	3 (1)	0	0
Skin and subcutaneous tissue disorders				
Erythema	5 (0.9)	3 (1)	2 (0.7)	0

*TEAEs are for subjects who received EUFLEXXA in both the core and extension (219 out of 433).
N = number of subjects in a given treatment group for the population analyzed; n = number of subjects reporting at least 1 AE within system organ class/preferred term; (%) = percentage of subjects based on N; TEAE = treatment-emergent adverse event.
Note: Related AEs are AEs with study device relationship classified as "Certain," "Probable," "Possible" or "Un-assessable."

Twenty-three serious TEAEs were reported in 19 (3.2%) subjects during the study: 10 (3.4%) subjects in the EUFLEXXA group and 9 (3.1%) subjects in the saline group. One of these events was considered related to the study device (increased redness of the left knee joint in the EUFLEXXA group). Eight (1.4%) subjects had 9 TEAEs leading to discontinuation: 3 (1.0%) subjects in the EUFLEXXA group and 5 (1.7%) subjects in the saline group.

Twelve (2.8%) subjects reported 20 serious TEAEs during the extension phase. Six of these subjects had received EUFLEXXA during the core study. None of the serious TEAEs was considered related to study device, and all resolved. Two (0.5%) subjects had TEAEs leading to discontinuation from the study, one of whom received EUFLEXXA during the core study; both subjects had events that were considered unrelated to study device.

Two subjects on saline experienced joint effusion. There were no reports of joint effusion among subjects receiving EUFLEXXA during the core and extension phase.

CLINICAL STUDIES
12 Week Multicenter Clinical Study
The safety and effectiveness of EUFLEXXA as a treatment for pain in OA of the knee was investigated in a multicenter clinical trial conducted in Germany.

Study Design
The clinical investigation was a prospective randomized, double-blinded, active control (commercially available hyaluronan) study conducted at 10 centers in Germany. A total of 321 patients with stage 2 – 3 osteoarthritis of the knee according to the Kellgren and Lawrence grading system, meeting the Altman Criteria for Classification of Idiopathic Osteoarthritis of the knee, and scoring an average score of 41 – 80 mm on the WOMAC VAS pain index were randomized into groups of equal size to receive either EUFLEXXA (160 patients) or the active control (161 patients).

Patient Population and Demographics
The demographics of trial participants were comparable across treatment groups with regard to age, gender, Kellgren and Lawrence grading system, stiffness, crepitus, bony enlargement, and no palpable warmth. Table 5 lists the demographics of the patient population.

Table 5. Patient Baseline Characteristics

Parameters	Number of Patients (%)	
	EUFLEXXA	Active Control
† Kellgren and Lawrence Grading System		
Definite osteophytes (Stage 2) Moderate multiple osteophytes (Stage 3)	88 (55.0%) 72 (45.0%)	84 (52.2%) 77 (47.8%)
Study knee Left Right	73 (45.6%) 87 (54.4%)	80 (49.7%) 81 (50.3%)
Age (n = number of patients)	62.7 ± 7.5 (160)	3.7 ± 7.3 (161)
Female (n)	62.9 ± 7.9 (99)	64.3 ± 7.3 (108)
Male (n)	62.5 ± 6.8 (61)	62.5 ± 7.3 (53)
Osteoarthritis duration Study knee (months prior to enrollment)	57.1 ± 45.9	60.7 ± 53.5
Radiological diagnosis Study knee (months prior to enrollment)	3.9 ± 3.8	4.4 ± 6.4
‡ Altman Criteria		
Knee pain	160 (100%)	161 (100%)
Stiffness < 30 minutes	151 (94.4%)	151 (93.8%)
Crepitus	154 (96.3%)	159 (98.8%)
Bony tenderness	134 (83.8%)	145 (90.1%)
Bony enlargement	72 (45.0%)	76 (47.2%)
No palpable warmth	153 (95.6%)	149 (92.5%)

† Kellgren and Lawrence (Ann Rheum Dis 1957;(16):494-501): Based on radiological findings, osteoarthritis stages were defined as follows: 0 = normal, 1 = doubtful narrowing of joint space and possible osteophytic lipping, 2 = definite osteophytes and possible narrowing of joint space, 3 = moderate multiple osteophytes and definite narrowing of joint space, some sclerosis and possible deformity of bone contour, 4 = large osteophytes, marked narrowing of joint space, severe sclerosis and definite deformity of bone contour.

‡ Altman, et al., (Arthritis and Rheumatism 1986;29(8):1039-1049): Clinical criteria for classification of idiopathic osteoarthritis (OA) of the knee were defined as follows: Knee pain and at least 3 of the following 6 parameters: Age > 50 years, Stiffness < 30 minutes, Crepitus, Bony tenderness, Bony enlargement, No palpable warmth.

Clinical Results
For this trial, the main performance analysis for determining non-inferiority was determined using the improvement in the average of the five patient's self-evaluation pain parameters measured by the VAS WOMAC index at Week 12 from baseline. This analysis was performed for both the intent-to-treat population, (i.e., every subject who received the injection), and the evaluable population, (i.e., those subjects who had average pain scores of 41-80

PATIENT INFORMATION
EUFLEXXA®
(1% sodium hyaluronate)

Be sure to read the following important information carefully.
This information does not take the place of your doctor's advice. If you do not understand this information or want to know more, ask your doctor.

TABLE OF CONTENTS

WHAT IS THE EUFLEXXA PRODUCT?
EUFLEXXA is a gel-like, elastic, sterile product containing natural, highly purified hyaluronan (pronounced hye-a-loo-ROE-nan). Hyaluronan is a natural substance found in the body. It is present in particularly high amounts in joint tissues and in the fluid that fills the joints. The body's own hyaluronan acts like a lubricant and a shock absorber in the joint. It is needed for the joint to function properly.

Unlike some other hyaluronan products, EUFLEXXA does not come from bird-derived sources.

WHAT IS EUFLEXXA USED FOR?
EUFLEXXA is used to relieve knee pain due to osteoarthritis (pronounced Os-tee-oh-are-THRY-tis). It is used for patients who do not get enough relief from simple pain medications such as acetaminophen or from exercise and physical therapy.

Osteoarthritis is a condition that involves the wearing down of cartilage (the protective covering on the ends of your bones). In osteoarthritis, there may not be enough or a decrease in the quality of the gel-like substance in the joint and surrounding tissues.

HOW IS EUFLEXXA GIVEN?
EUFLEXXA comes in pre-filled syringes containing 2 mL (about half a teaspoon) of product. EUFLEXXA is given by injection directly into the knee joint by a doctor or other qualified healthcare professional. EUFLEXXA is injected into your knee once a week, for a total of three injections.

ARE THERE ANY REASONS WHY I SHOULD NOT TAKE EUFLEXXA?
Your doctor will determine if you are not an appropriate candidate for EUFLEXXA.
- Do not take EUFLEXXA if you have had previous allergic reactions to EUFLEXXA or hyaluronan products.
- EUFLEXXA should not be injected into the knee if you have a knee joint infection or skin diseases or infections around the injection site.

WHAT SHOULD MY DOCTOR WARN ME ABOUT?
- EUFLEXXA has not been tested in pregnant women or women who are nursing. Tell your doctor if you think you are pregnant or nursing a child before agreeing to be injected with EUFLEXXA.
- EUFLEXXA has not been tested in children less than 18 years of age.

WHAT ARE THE RISKS OF GETTING EUFLEXXA INJECTIONS? (ADVERSE EFFECTS)
The following is a list of adverse effects that can occur with either EUFLEXXA or saline injections.

Adverse Effect	Likelihood of Adverse Effect Based on the 26 Week Clinical Study
Joint pain	62 out of 588 subjects had joint pain
Back pain	23 out of 588 subjects had back pain
Limb/muscle pain	23 out of 588 subjects had limb/muscle pain
Joint swelling	8 out 588 subjects had joint swelling

If you have a reaction where the swelling is extensive and painful, you should call your doctor.

WHAT ARE THE BENEFITS OF EUFLEXXA INJECTIONS?
Based on the clinical studies, EUFLEXXA subjects had pain relief and improvement in function lasting up to 6 months.

WHAT SHOULD I DO AFTER RECEIVING A EUFLEXXA INJECTION?

- Avoid physical activity for 48 hours following the injection to keep your knee from swelling.
  Some examples of activities to avoid include:
  - Running - Tennis - Hiking
  - Jumping - Swimming - Heavy lifting (weight lifting)
  - Jogging - Bicycling - Aerobic exercise
- Do not stand on your feet for more than one hour at a time during the first 48 hours following your injection of EUFLEXXA.
- You should ask your doctor when you should begin major physical activities again.

WHEN SHOULD I CALL MY DOCTOR? (TROUBLESHOOTING)

If you experience any of the adverse effects or symptoms described earlier or if you have any other problems, you should call your doctor immediately.

WHAT OTHER NON-SURGICAL TREATMENTS ARE AVAILABLE FOR OSTEOARTHRITIS?

If you have osteoarthritis, there are other non-surgical treatment options available and these include:

- **Non-drug treatments**
  - Avoiding activities that cause pain in your knee
  - Exercise
  - Physical therapy
  - Weight loss (if overweight)
  - Removal of excess fluid from the knee
- **Drug therapy**
  - Pain medications such as acetaminophen or stronger prescription medications
  - Drugs that reduce inflammation, such as aspirin and other nonsteroidal anti-inflammatory agents (NSAIDs) such as ibuprofen and naproxen
  - Corticosteroids that are injected directly into the joint

WHAT DID CLINICAL STUDIES WITH EUFLEXXA SHOW?

A medical study involving 321 patients with knee pain due to osteoarthritis was performed in Germany. The study compared EUFLEXXA against another hyaluronan once a week for 3 weeks (control arm).

Pain, stiffness and function of the knee joint and patients' and doctors' judgment of treatment success were measured for 12 weeks. Patients were those with knee paindue to osteoarthritis who had not received pain relief with other medications. Patients experienced pain relief from EUFLEXXA injections similar to those patients in the control arm.

Another study involving 588 patients with knee pain due to osteoarthritis was conducted in the United States. Two hundred ninety three (293) patients were injected with EUFLEXXA and 295 with saline (salt water). The pain scores were used to compare the effectiveness of EUFLEXXA to saline injection: Patients were asked to rate how pain was felt on the 100 mm scale after 50 foot walk at 1, 2, 3, 6, 12, 18 and 26 weeks. EUFLEXXA group improved 25.7 mm from the baseline pain score, whereas the saline group improved 18.5 mm. There was more improvement in EUFLEXXA group than the saline group. The difference was 6.6 mm on 100 mm pain scale in favor of EUFLEXXA group. Study results showed significant improvement in osteoarthritis knee pain relief with EUFLEXXA therapy lasting up to 6 months. The study also showed that a repeated cycle of EUFLEXXA for an additional 26 weeks (1 year total) was safe.

EUFLEXXA has not been proven to relieve pain in any other joints.

WHAT ADVERSE EVENTS WERE OBSERVED IN THE CLINICAL STUDIES?

The number of subjects reporting adverse events was generally similar between the EUFLEXXA and Saline groups. Serious events were not observed in these clinical studies.

The following are the most common adverse events and symptoms that occurred during clinical studies of EUFLEXXA:

- Pain in the knee or at the injection site
- Stiffness, swelling or warmth in or around the knee

HOW DO I GET MORE INFORMATION ABOUT EUFLEXXA? (PATIENT ASSISTANCE)

If you have any questions or problems, talk to your doctor. If you would like more information on EUFLEXXA, please call 1-888-FERRING (1-888-337-7464) toll-free or visit www.euflexxa.com.

MANUFACTURED FOR:
FERRING PHARMACEUTICALS INC.
PARSIPPANY, NJ 07054

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allowing only one parameter to be below 20 or above 80 at both the pre-screening visit and visit 1). For those patients who dropped out of the study before Week 12, the last evaluation was used. For those patients who requested NSAID or analgesic during the study, the last evaluation before start of NSAID/analgesic was used for the analysis. The results indicate that the effect of EUFLEXXA on pain relief was not inferior to that of a commercially available hyaluronan.

Table 6. Changes from Baseline to Last Visit in Overall Pain Score (primary end point, average of five pain scores)

	EUFLEXXA		Active Control (commercially available hyaluronan)		Standard Deviation	P value (non-inferiority)
	N	Change from Baseline (mm)	N	Change from Baseline (mm)		
ITT – patient	160	29.9	161	28.4	21	0.0032
Evaluable – patient	103	33.5	105	32.18	20	0.0083

26 Week Multicenter Clinical Trial

This was a multicenter, randomized, double-blind trial evaluating the efficacy and safety of EUFLEXXA as compared to saline comparator in subjects with chronic osteoarthritis of the knee. The intervention consisted of three weekly injections into the target knee with evaluations from baseline through Week 26 (1, 2, 3, 6, 12, 18, and 26). The primary objective was to demonstrate superiority over saline comparator from baseline to Week 26 using the pain level reported following a 50 foot walk test, measured by 100 mm visual analog scale. The following secondary endpoints were also evaluated: OARSI responder rate at Week 12 and Week 26; WOMAC pain, disability, and joint stiffness score changes from baseline to Week 12 and 26; and change in Patient Global Assessment from baseline to Week 12 and Week 26.

Patient Population and Demographics

A total of 821 subjects were screened for the study, and 588 subjects were randomized. Approximately 88% of the randomized subjects completed the study, with similar proportions completing in each treatment group. Sixty-eight (11.6%) subjects discontinued the randomization/treatment phase prematurely: 34 (11.5%) in the saline group and 34 (11.6%) in the EUFLEXXA group. The most common reasons for discontinuation were the subject's withdrawing consent 25 (4.3%) and AEs 17 (2.9%). A total of 433 (73.6%) subjects entered the open-label extension study.

Clinical Results

Primary Endpoint

In the primary efficacy analysis, the EUFLEXXA group showed a larger mean decrease in pain scores on the 50-foot walk test from baseline to Week 26 than the saline group: –25.7 (28.85) mm versus –18.5 (32.53) mm, respectively. The group difference in least squares mean change from baseline of -6.6 mm (95% CI = –10.8 to –2.5 mm) was statistically significant (p-value = 0.002). Figure 1 depicts the adjusted mean change in pain scores on 50-foot walk test from baseline to week 26 (ITT Population).

Table 7. The Adjusted Mean Change in Pain Scores on 50-foot Walk Test from Baseline to Week 26 (ITT[a] Population).

	Change from Baseline at Week 26		Difference in Changes (EUFLEXXA - Saline) from Baseline[b,c,d]	2-Sided 95% Lower and Upper Bound of Confidence Interval of the Difference[d] in Changes[c]	2-Sided P-Value[c]
	Saline (n=295) (SD)	EUFLEXXA (n=291) (SD)			
50-foot walk test, measured on a 100mm horizontal VAS score improvement at 26 weeks	–18.5 (32.53)	–25.7 (28.85)	–6.6 mm	–10.8, –2.5	0.002

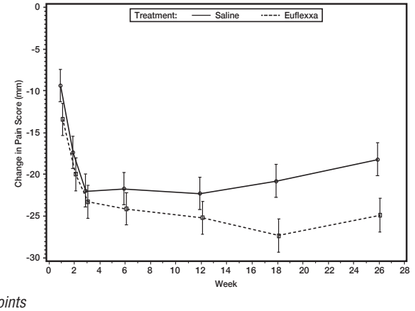
[a] ITT= Intent to Treat

[b] Negative (–) values favor EUFLEXXA.

[c] The analysis is based on repeated measure mixed model Analysis of Covariance (ANCOVA) from baseline through 26 weeks on mean change from baseline 50-foot walk test, measured on a 100mm horizontal VAS score improvement at 26 weeks, with a weekly injection of EUFLEXXA for 3 weeks.

[d] difference = least squares mean difference

Figure 1 Adjusted Mean Change in Pain Scores on 50-foot Walk Test from Baseline to Week 26 (ITT Population)



Secondary Endpoints

Table 8. OARSI Responder Rates Using 50-foot Walk Test (ITT)

Visit Response/Statistics	Saline N=295	EUFLEXXA N=291	All Treatments N=586	Overall Comparison (2-sided 95% Lower and Upper Bound Statistics of Confidence Interval of Odds Ratio)[c]
Week 12				
No. of subjects with data	274	263	537	
Yes-n (%)	167 (60.9)	173 (65.8)	340 (63.3)	
No-n (%)	107 (39.1)	90 (34.2)	197 (36.7)	
Odds ratio[a] (95% CI)				1.3 (0.9, 1.8)
P-value				0.202
Week 26				
No. of subjects with data	264	254	518	
Yes-n (%)	155 (58.7)	169 (66.5)	324 (62.5)	
No-n (%)	109 (41.3)	85 (33.5)	194 (37.5)	
Odds ratio[b] (95%CI)				1.4 (1.0, 2.1)
P-value				0.047

OARSI = Osteoarthritis Research Society International; ITT = intent-to-treat; N = number of subjects in a given treatment group for the population analyzed; n = number of subjects; (%) = percentage of subjects based on N; CI = confidence interval.

Note: The p-value for the odds ratio corresponds to the Wald chi-square test for EUFLEXXA versus saline with respect to OARSI responder rates from a logistic regression adjusting for treatment group and study center.

Note: A subject was considered a responder if there was high improvement in pain or function >50% and absolute change >20 mm or improvement in at least two of the three following categories: pain >20% and absolute change >10 mm, function >20% and absolute change >10 mm, and/or Patient Global Assessment >20% and absolute change >10.

[a,b] $_{\beta\ (\text{Log Odds Ratio})}$ = 1.27 for 12 weeks and 1.4 for 26 weeks, based on a logistic regression model (Log Odds Ratio)=$\log_e$[probability (responder)/probability (non-responder)] $_{\text{EUFLEXXA}}$ / [probability (responder)/probability(non-responder)]$_{\text{saline}}$

[c] When odds ratio >1, [probability(responder)/probability (non-responder)] $_{\text{EUFLEXXA}}$ > [probability (responder)/probability (nonresponder)$_{\text{saline}}$]

Table 9. Other Secondary Endpoints at 26 Weeks for ITT (n=291)

	Change from Baseline at Week 26		The Difference[d] in Changes (EUFLEXXA - Saline) from the Baseline[b]	2-Sided Test P-Value[a]
	Saline (SD) (n=295)	EUFLEXXA (SD) (n=291)		
WOMAC C[c] (disability)	–14.6 (25.79)	–19.5 (24.68)	–4.3 mm	0.019
WOMAC B (joint stiffness)	–15.4 (29.33)	–19.6 (31.27)	–3.8 mm	0.075
WOMAC A (pain)	–16.3 (26.82)	–19.2 (26.81)	–3.3 mm	0.085
Patient Global Assessment	–17.8 (28.82)	–22 (30.38)	–4.5 mm	0.035

Note: The analysis is based on repeated measure mixed model Analysis of Covariance (ANCOVA) from baseline through 26 weeks on mean change from baseline.

[a] P-values are not adjusted for the multiplicity.

[b] Negative (–) values for WOMAC C and Patient Global Assessment are in favor of EUFLEXXA.

[c] The Western Ontario and McMaster Universities Arthritis Index (WOMAC) is a set of standardized questionnaires used by healthcare professionals to evaluate the condition of patients with osteoarthritis of the knee and hip. WOMAC Pain Scale is 100mm.

[d] difference=least square mean difference

No significant treatment group differences were observed in the change in number of study-specific acetaminophen tablets used per week or in the proportion of subjects who were pain free at Week 26 or last visit.

DETAILED DEVICE DESCRIPTION

Each syringe of EUFLEXXA contains:

Sodium hyaluronate	20 mg
Sodium chloride	17 mg
Disodium hydrogen phosphate dodecahydrate	1.12 mg
Sodium dihydrogen phosphate dihydrate	0.1 mg
Water for injection	q.s.

INTERACTIONS

None currently known

HOW SUPPLIED

EUFLEXXA is supplied in 2.25 mL nominal volume, disposable, pre-filled glass syringes containing 2 mL of EUFLEXXA. Only the contents of the syringe are sterile. EUFLEXXA is nonpyrogenic.
This product is not made with natural rubber latex.
Product Number: 55566-4100-1
3 disposable syringes per carton

STORAGE INSTRUCTIONS

Do not use EUFLEXXA if the package is open or damaged. Store in the original package at 2°-25°C (36°-77°F). Protect from light. Do not freeze.

CAUTION

Federal law restricts this device to sale by or on the order of a physician.

DIRECTIONS FOR USE

1. Each package of EUFLEXXA is manufactured using aseptic filling techniques. Do not use if the blister package is opened or damaged.
2. Remove joint effusion, if present.
3. Peel off the blister Tyvek backing (The syringe should be used immediately after the individual syringe blister is opened).
4. While holding the blister open side down, bend the blister and allow the syringe to fall gently onto the clean surface. Alternatively, hold the blister open side up and bend back the blister until the barrel's luer end is exposed. Gripping the luer end of the barrel, remove the syringe from the blister. **Do not remove the syringe from the plunger end.**
5. Remove the tip cap from the syringe and attach an appropriately sized sterile needle, for example 17 to 21 gauge.
   Attention: Do not apply pressure to the plunger rod while the needle is being affixed. Verify that the needle is properly locked to the Luer Lock Adapter (LLA). Do not overtighten the LLA; this can lead to loosening of the LLA from the barrel.
6. Apply gentle pressure to the plunger in order to expel air from the syringe needle and to verify that the syringe is operating properly.
7. The syringe is ready for use.
8. Inject intra-articularly into the knee synovial capsule using strict aseptic injection procedures. Inject the full syringe contents, 2 ml into one knee only. If treatment is being administered to both knees, use a separate syringe for each knee. Discard any unused EUFLEXXA.
9. For single use only. Do not resterilize.
10. Store at 2°-25°C (36°-77°F). Protect from light. Do not freeze. If refrigerated, remove from refrigeration at least 20-30 minutes before use.
11. A dose of 2 ml is injected intra-articularly into the affected knee at weekly intervals for three weeks, for a total of three injections.

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PARSIPPANY, NJ 07054

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