

A close-up photograph of a person's knee, showing the skin and joint. A vibrant blue powder is splashing and settling around the knee, creating a dynamic and energetic visual. The background is a light blue gradient with diagonal lines.

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 site²
- Avoid standing on your feet for more than 1 hour at a time during the first 48 hours following the injection²
- Ask your healthcare provider when you should begin major physical activities again²
- Call your doctor immediately if you experience joint pain, back pain, limb/muscle pain, joint swelling, or any other problems²



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.²
- 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.

Please see enclosed Full Prescribing Information in pocket.

FERRING
PHARMACEUTICALS

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 **euflexxa**®
1% SODIUM HYALURONATE

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 pain due 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.

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6309501103 Rev. 07/2016

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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: OARS1 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 ^e	2-Sided P-Value ^e
	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

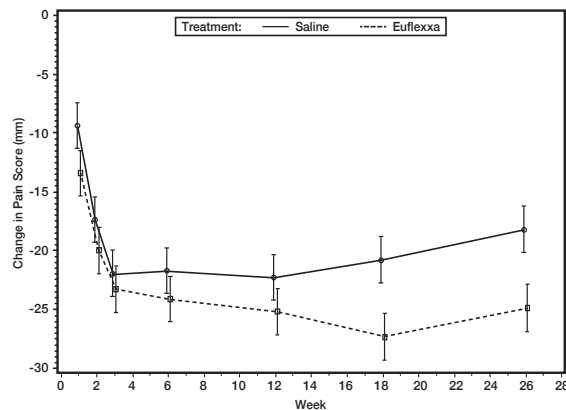
^a ITT= Intent to Treat

^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. OARS1 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

OARS1 = 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 OARS1 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 P_g (Log Odds Ratio) = 1.27 for 12 weeks and 1.4 for 26 weeks, based on a logistic regression model

(Log Odds Ratio) = \log [probability (responder)/probability (non-responder)]_{EUFLEXXA} / [probability (responder)/probability (non-responder)]_{saline}

^c When odds ratio > 1, [probability (responder)/probability (non-responder)]_{EUFLEXXA} > [probability (responder)/probability (non-responder)]_{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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