# GET BACK IN THE GAME GUIDE

What you need to know about how EUFLEXXA® could help reduce pain associated with osteoarthritis (OA) of the knee so you can get back to what matters to you.

This guide is provided by



#### 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.

# GET BACK IN THE GAME GUIDE



# WHAT YOU'LL FIND INSIDE

# Continue scrolling or click below to go directly to each section:

- 1. So, what is osteoarthritis (OA) of the knee?
- 2. Why are hyaluronic acid (HA) injections such a big deal?
- 3. The scoop on EUFLEXXA: an HA injection treatment for OA of the knee
- 4. Getting back in the game with EUFLEXXA
- **5.** Important Safety Information

## 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.



# SO, WHAT IS OSTEOARTHRITIS (OA) OF THE KNEE?

Osteoarthritis is a disease that gets worse over time and primarily affects the weight-bearing joints of the body, with the knees being the most frequently affected joint.<sup>1</sup> It is estimated that approximately 37% of adults over the age of 60 are affected by osteoarthritis of the knee.<sup>2</sup> The disease is expected to become even more common due to an increase in obesity and because people are living longer.<sup>1,3</sup>

Factors that might make a person more likely to experience OA of the knee include age, sex, body mass index, and previous injuries to the knee such as ligament tears.<sup>4</sup> The symptoms most associated with OA are joint pain and a loss of joint function, along with the breaking down of the cartilage in the knee.<sup>3,5</sup> Osteoarthritis is the most common form of chronic arthritis, affecting 240 million people around the world.<sup>6</sup>

### Healthy knee joint





Because OA is a disease that gets worse over time, it can lead to a decrease in knee function which can, in turn, limit one's ability to perform regular activities.<sup>5</sup>

Read on to learn about treatment options for OA of the knee and how EUFLEXXA<sup>®</sup> can help.

### **IMPORTANT SAFETY INFORMATION (continued)**

• EUFLEXXA has not been tested in pregnant women, women who are nursing or in 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).



EUFLEXXA® is the #1 prescribed hyaluronic acid (HA) injection.<sup>7</sup>

# **Treating OA of the Knee**

If you've been diagnosed with OA of the knee, you're not alone. It is a fairly common condition and, while there is no cure for it, you certainly do not just have to accept that knee pain is going to be a part of your life. There are treatments that can help with the symptoms of OA of the knee, such as HA injections, like EUFLEXXA. Most doctors typically recommend a combination of treatments designed to relieve pain and maximize the function and movement of the knee.<sup>3</sup>

You may have already tried treatments such as over-the-counter or prescription pain relievers for your OA of the knee. Another common treatment your doctor may recommend is a corticosteroid injection. These can provide short-term pain relief but may result in side effects such as pain, stiffness, and swelling of the joint. Corticosteroid injections are also a potential concern for patients with diabetes.<sup>5,8,9</sup>

Hyaluronic acid (HA) injections are another possible treatment for OA of the knee. Here are some of the potential benefits of HA injections<sup>10</sup>:

- Provide pain relief from OA of the knee
- Offer significant improvements in pain and physical function
- Have a low incidence of complications
- Are well tolerated
- Can help reduce the breakdown of the knee joint
- Provide significant reduction in inflammation and swelling

Additionally, clinical studies have shown that incorporating HA injections in the early stages of OA of the knee can help reduce its associated symptoms.<sup>11</sup>

## Continue scrolling to learn how hyaluronic acid injections like EUFLEXXA are used to treat OA of the knee

### **IMPORTANT SAFETY INFORMATION (continued)**

• The most common adverse events related to EUFLEXXA injections were joint pain, back pain, limb pain, muscle pain, and joint swelling.



# WHY ARE HYALURONIC ACID (HA) INJECTIONS SUCH A BIG DEAL?

Hyaluronic acid (HA) is found naturally throughout the body, but it is very prevalent in the knee joint where it works with the natural knee fluid to cushion and lubricate the knee so it can withstand the demands of daily life.<sup>5,12</sup> The HA that occurs naturally in the body has a high molecular weight, which means it is thick, sticky, and elastic-like, and helps with shock absorption and cushioning of the knee. When the molecular weight of the natural HA in the knee decreases, the result can lead to increase in pain, swelling, and the risk of knee injury.<sup>4</sup>

EUFLEXXA® is a highmolecular-weight HA that provides shock absorption and lubrication of the knee joint.<sup>5</sup>

# The Benefits of HA Injections

The pain and swelling associated with OA of the knee can be very frustrating, especially for people who are used to living an active lifestyle. There are treatments that may give those patients the freedom to continue being active. One of these treatment options is hyaluronic acid injections.

Hyaluronic acid injections, like EUFLEXXA<sup>®</sup>, are treatments administered by your doctor and are injected directly into the knee. Research has shown that HA injections can help restore the loss of HA in the knee and can have several positive results.<sup>5</sup>

## Keep reading to see how EUFLEXXA could help you get back in the game!

#### **IMPORTANT SAFETY INFORMATION (continued)**

Do not take this product if you have had any previous allergic reaction to EUFLEXXA or hyaluronan products.



# THE SCOOP ON EUFLEXXA: AN HA INJECTION TREATMENT FOR OA OF THE KNEE

EUFLEXXA is the #1-prescribed HA injection and closely resembles the HA found naturally in the knee.<sup>7,13</sup>

# The Benefits of EUFLEXXA: Getting You Back in the Game<sup>14</sup>



Most common adverse events in the clinical trial include joint pain (11/160), increase in blood pressure (3/160), joint swelling (3/160), feeling of sickness (3/160), tingling (2/160), back pain (1/160), nausea (1/160), skin irritation (1/160).<sup>15</sup>



*"I began experiencing relief from pain about six to eight weeks after injection [1 round of EUFLEXXA] until all of a sudden I realized I had no pain in my knee."* 

**Jan O.** EUFLEXXA patient

Individual results may vary.

### **IMPORTANT SAFETY INFORMATION (continued)**

 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.



# **Proven Results With EUFLEXXA®**

Treatment with EUFLEXXA consists of an injection given by your doctor, once a week, for 3 consecutive weeks.<sup>15</sup> In fact, in a clinical trial, patients taking EUFLEXXA saw a 62% improvement in knee pain after 12 weeks.<sup>16</sup> Treatment with HA injections such as EUFLEXXA may also allow you to delay more invasive treatments and procedures in the future.<sup>9</sup>



Most common adverse events in the clinical trial include joint pain (11/160), increase in blood pressure (3/160), joint swelling (3/160), feeling of sickness (3/160), tingling (2/160), back pain (1/160), nausea (1/160), skin irritation (1/160).<sup>15</sup>

# After 3 injections, clinical trial patients injected with EUFLEXXA had significantly less pain associated with 5 basic functions.<sup>16</sup>





WALKING





So a

RESTING AT NIGHT

# Scroll to next page to learn more about the efficacy and safety of EUFLEXXA!

## **IMPORTANT SAFETY INFORMATION (continued)**

• EUFLEXXA has not been tested in pregnant women, women who are nursing or in 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).



# **EUFLEXXA® CLINICAL TRIAL DATA**

In the clinical trial, patients injected with EUFLEXXA reported, on average, a 62% improvement in knee pain compared with 55% of patients using another HA product.<sup>16</sup> Additionally, significantly fewer patients taking EUFLEXXA for treatment of pain in one knee reported a need for acetaminophen compared with patients taking the other product.<sup>16</sup> In fact, 3 times more patients treated with EUFLEXXA for OA pain in one knee avoided taking pain medication compared with patients treated with the other product.<sup>15</sup>

# In a clinical trial, approximately 2 out of 3 EUFLEXXA patients were **pain-free**<sup>\*</sup> **at 12 weeks**<sup>16</sup>

# 81% of patients

treated with EUFLEXXA were satisfied with the reduction in OA associated knee pain<sup>16</sup>

\*Based on % reduction in WOMAC pain score from baseline in a pivotal, 12-week trial of EUFLEXXA (n=157) vs Synvisc (n=158). Pain-free is defined as symptom-free for the 5 WOMAC pain questions (with average visual analog scale [VAS] scores of <20 mm).<sup>16</sup>

WOMAC=Western Ontario and McMaster Universities Osteoarthritis Index.

# Once your doctor recommends EUFLEXXA:

Schedule 3 injection appointments

- Avoid physical activity for 48 hours after injection
- Ice your knee if you have mild pain or swelling



After 6 months, follow up with your doctor to determine if repeat treatment is needed



*"I will recommend EUFLEXXA as my hyaluronic acid of choice as an option for treating a patient's knee osteoarthritis and reducing their pain and inflammation."* 

Eric I. Ferkel, MD Southern California Orthopedic Institute

### IMPORTANT SAFETY INFORMATION (continued)

• The most common adverse events related to EUFLEXXA injections were joint pain, back pain, limb pain, muscle pain, and joint swelling.



# **GETTING BACK IN THE GAME WITH EUFLEXXA®**

# Osteoarthritis (OA) of the Knee Pain Self-Assessment

Complete and print this self-assessment questionnaire to share with your doctor.

**NOTE:** This assessment tool can aid your doctor in the diagnosis and treatment of OA of the knee but does not claim to provide an accurate diagnosis. This form should only be used as a guide.

## How long have you experienced knee pain?

Less than 1 month 1 to 3 months 3 to 6 months 6 to 12 months More than 12 months

# How have you tried to manage your

# knee pain?

Ice Over-the-counter pain relievers Exercise Physical therapy Other

# What activities are most affected by your

## knee pain? *Select all that apply* Sitting Climbing stairs Walking Standing

Sleeping

How often do you experience knee pain? Rarely Occasionally Frequently All the time

## How much does your knee pain affect your level of activity? Not at all

Somewhat Very much All the time

Please see complete Indication, Important Safety Information, and Full Prescribing Information at www.euflexxa.com



# **Doctor Discussion Guide**

Use these questions to help start the OA of the knee and treatment discussion with your doctor.

- 1. What caused my OA of the knee?
- 2. Will taking a pain reliever help with my OA of the knee?
- 3. Are there any exercises I can do to help strengthen my knee joint?
- 4. Will yoga or stretching help my knee feel better?
- 5. Does the weather have any impact on how my knee feels?
- 6. Is a hyaluronic acid injection such as EUFLEXXA a treatment option for me?

#### 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 in 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.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.FDA.gov/medwatch or call 1-800-FDA-1088.

You may also contact Ferring Pharmaceuticals Inc. at 1-888-FERRING.

### **Click for Full Prescribing Information.**

REFERENCES: 1. Webner D, Huang Y, Hummer C. Intraarticular hyaluronic acid preparations for knee osteoarthritis: are some better than others? Cartilage. 2021;30(Suppl 1):16195-16365. 2. Grace L, McAlindon T, Hawker G, et al. Symptom assessment in knee osteoarthritis needs to account for physical activity level. Arthritis Rheumatol. 2015;67(11):2897-2904. 3. Altman R, Rosen J, Bloch D, et al. A double-blind, randomized, saline-controlled study of efficacy and safety of EUFLEXXA® for treatment of painful osteoarthritis of the knee, with an open-label safety extension (the FLEXX trial). Semin Arthritis Rheum. 2009;39(1):1-9. 4. Nicholls M, Manjoo A, Shaw P, et al. Rheological properties of commercially available hyaluronic products in the United States for the treatment of osteoarthritis knee pain. Clin Med Insights Arthritis Musculoskelet Disord. 2018;11:1-5. 5. Altman RD, Manjoo A, Fierlinger A, et al. The mechanism of action for hyaluronic acid treatment in the osteoarthritic knee: a systematic review. BMC Musculoskeletal Disorders. 2015;16(321):1-10. 6. Nelson A. Osteoarthritis year in review 2017: clinical. Osteoarthritis Cartilage. 2018;26:319-325. 7. Rolling 12 month average of IQVIA claims data based on unique patients (November 2021). 8. Arroll B, Goodyear-Smith F. Corticosteroid injections for osteoarthritis of the knee: meta-analysis. BMJ. 2004;10(328):1-5. 9. Kompell A, Roemer F, Murakami A, et al. Intra-articular corticosteroid injections in the hip and knee: perhaps not as safe as we thought? Radiology. 2019;293:656-663. 10. Migliore A, Procopio S. Effectiveness and utility of hyaluronic acid in osteoarthritis. Clin Cases Miner Bone Metab. 2015;12(1):31-33. 11. Bowman S, Awad M, Hamrick M, et al. Recent advances in hyaluronic acid based therapy for osteoarthritis. Clin Trans Med. 2018;7(6): 1-11. 12. Sirin D, Kaplan N, Yilmaz I, et al. The association between different molecular weights of hyaluronic acid and CHAD, HIF-1α, COL2A1 expression in chondrocyte cultures. Exp Ther Med. 2018;15:4205-4212. 13. Nicholls M, Manjoo A, Shaw P, et al. A comparison between rheological properties of intra-articular hyaluronic acid preparations and reported human synovial fluie. Adv Ther. 2018;35:523-530. 14. Moreland L. Intra-articular hyaluronan (hyaluronic acid) and hylans for the treatment of osteoarthritis: mechanism of action. Arthritis Res Ther. 2003;5:54-67. 15. EUFLEXXA [package insert]. Parsippany, NJ: Ferring Pharmaceuticals Inc. 16. Kirchner M, Marshall D. A double-blind randomized controlled trial comparing alternate forms of high molecular weight hyaluronan for the treatment of osteoarthritis of the knee. *Osteoarthritis Cartilage*. 2006;14(2):154-162.

FERRING and the FERRING PHARMACEUTICALS logo are trademarks of Ferring B.V. EUFLEXXA® is a registered trademark of Ferring B.V. © 2023 Ferring B.V. All rights reserved. US-EU-2200069





#### PRODUCT INFORMATION **EUFLEXXA®**

(1% sodium hyaluronate)

10 mg 8.5 mg

0.56 ma

0.05 mg

q.s.

#### CONTENT

Ead

ch 1 mL of EUFLEXXA contains:	
Sodium hyaluronate	
Sodium chloride	
Disodium hydrogen phosphate dodecahydrate	
Sodium dihydrogen phosphate dihydrate	
Water for injection	

#### 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  $\beta \rightarrow 1,3$  and  $\beta \rightarrow 1,4$  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

		Patients	s, n (%)
Body System	ADE	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)
	Arthralgia	14 (8.75)	17 (10.6)
	Arthrosis	2 (1.25)	0
	Back pain	8 (5.00)	11 (6.83)
Musculoskeletal, connective tissue and bone	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  $\geq$  2% among treatment groups.

#### Table 3: Treatment-Emergent Adverse Events by Preferred Term with an Incidence of $\ge 2\%$ among the **Treatment Groups (Safety Population**

	26 Week FLEXX	Study (Core)		Extension Study Repeat Injection for 52 Weeks*
System Organ Class Preferred Term	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 comp	lications			
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 leastone adverse event within system organ class/preferred term: (%) = percentage of subjects based on N: TEAE = treatmentemergent 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  $\geq$  1 among Treatment Groups (Safety Population)

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

	26 Week FLE	XX Study (Core)	Extension Study Repeat Injection for 52 Weeks*	
System Organ Class Preferred Term	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 dis	orders			
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**

<u>12 Week Multicenter Clinical Study</u> 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 Desian

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 natients)

#### **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 (%)	
Farameters		EUFLEXXA	Active Control	
<sup>†</sup> Kellgren and Lawrence Gr	ading System			
Definite osteophytes (Stage	2)	88 (55.0%)	84 (52.2%)	
Moderate multiple osteophy	ytes (Stage 3)	72 (45.0%)	77 (47.8%)	
Study knee	Left	73 (45.6%)	80 (49.7%)	
	Right	87 (54.4%)	81 (50.3%)	
Age (n = number of patients	s)	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	ſ	160 (100%)	161 (100%)	
Stiffness < 30 minutes	Ī	151 (94.4%)	151 (93.8%)	
Crepitus	Ī	154 (96.3%)	159 (98.8%)	
Bony tenderness	Ī	134 (83.8%)	145 (90.1%)	
Bony enlargement	[	72 (45.0%)	76 (47.2%)	
No palpable warmth	ſ	153 (95.6%)	149 (92.5%)	

Kelloren 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 n 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?
- What is EUFLEXXA used for?
- How is EUFLEXXA given?
- Are there any reasons why I should not take EUFLEXXA?
- What should my doctor warn me about?
- What are the risks of getting EUFLEXXA injections? (Adverse Effects)
- . What are the benefits of EUFLEXXA injections?
- . What should I do after receiving a EUFLEXXA injection?
- When should I call my doctor? (Troubleshooting)
- What other non-surgical treatments are available for osteoarthritis? What did clinical studies with EUFLEXXA show?
- . What adverse events were observed in the clinical studies?
- How do I get more information about EUFLEXXA? (Patient Assistance)

### 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 birdderived 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 FUFI FXXA

- 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
- Hikina - Jumping - Swimming - Heavy lifting (weight lifting)
- Aerobic exercise
- Jogging Bicycling
- 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

6309501103 Rev. 07/2016 EUFLEXXA is a registered trademark of Ferring BV

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		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 EUELEXXA 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 baséline of -6.6 mm (95% Cl -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\* Population)

	Change from Baseline at Week 26		Difference in Changes (EUFLEXXA - Saline) from Baseline <sup>b.c.d</sup>	2-Sided 95% Lower and Upper Bound of Confidence Interval of the Difference <sup>d</sup> in Changes <sup>c</sup>	2-Sided P-Value°	
	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	

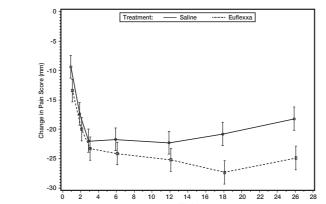
a ITT= Intent to Treat

<sup>b</sup> Negative (--) values favor EUFLEXXA

<sup>c</sup> 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.

<sup>d</sup> 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) <sup>e</sup>
Week 12	1			
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 <sup>a</sup> (95% CI)	1	ĺ	ĺ	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 <sup>b</sup> (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. <sup>be</sup> (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)]salin °When odds ratio >1, [probability(responder)/probability (non-responder)] EUFLEXXA > [probability (responder)/probability

(nonresponder)<sub>saline</sub>]

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

	Change from Baseline at Week 26		The Difference <sup>d</sup> in Changes	0 Cided Teet				
	Saline (SD) (n=295)	EUFLEXXA (SD) (n=291)	(EUFLEXXA - Saline) from the Baseline <sup>b</sup>	2-Sided Test P-Value <sup>a</sup>				
WOMAC 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

<sup>a</sup> P-values are not adjusted for the multiplicity

<sup>b</sup> Negative (-) values for WOMAC C and Patient Global Assessment are in favor of EUFLEXXA. 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

#### DETAILED DEVICE DESCRIPTION

ich 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 cartor

#### 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**

- 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
- Peel off the blister Tyvek backing (The syringe should be used immediately after the individual syringe 3 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.

- Apply gentle pressure to the plunger in order to expel air from the syringe needle and to verify that the 6 svringe is operating properly.
- 7. The syringe is ready for use.
- 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 8 a separate syringe for each knee. Discard any unused EUFLEXXA.
- 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

1)		









Toll free number for providers and patients to call with questions: 1-888-FERRING (1-888-337-7464).

# MANUFACTURED FOR:



FERRING PHARMACEUTICALS INC. PARSIPPANY. NJ 07054 Product Code: 55566-4100-1 6309501103 Rev. 07/2016 EUFLEXXA is a registered trademark of Ferring BV