

Product Code: 55566-4100-1

6122-05

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 a 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 studied.
- 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

- 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 and effectiveness of repeated treatment cycles of EUFLEXXA™ have not been established.

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 multicenter clinical trial conducted in Germany and a single center clinical trial that was conducted in Israel.

Multicenter Clinical Investigation

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)	14 (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

Single Center Study

In a single-center, single-blinded, placebo controlled, prospective, two parallel treatment arm clinical trial a total of 49 (25 EUFLEXXA™, 24 placebo) patients were randomized into two treatment groups in a ratio of 1:1 EUFLEXXA™ or placebo. Due to the limited number of patients that were enrolled in this investigation and differences in study design, conclusions concerning effectiveness could not be made, therefore, only the adverse events reported during the study were considered for evaluating the safety of this product.

Adverse events were reported by 17 (68%) of the patients in the EUFLEXXA™ group and 15 (63%) in the placebo group. Table 3 lists the adverse events that were reported during this study.

Table 3. Number of Adverse Events by Treatment Group

Term	EUFLEXXA™ n (%)	Placebo n (%)	Total
Knee pain	18 (53)	11 (35)	29
Upper respiratory tract infection	4 (12)	2 (7)	6
Back pain	2 (6)	1 (3)	3
Asthenia	1 (3)	2 (7)	3
Herpes simplex	1 (3)	0	1
Rash	1 (3)	1 (3)	2
Herpes zoster	1 (3)	0	1
Peptic ulcer	1 (3)	0	1
Rhinitis	1 (3)	0	1
Skeletal pain	1 (3)	0	1
Swollen eyelids	1 (3)	0	1
Total knee replacement	1 (3)	0	1
Knee swelling	1 (3)	0	1
Surgery	0	2 (7)	2
Knee trauma	0	1 (3)	1
Elective non-surgical procedures	0	1 (3)	1
Gingivitis	0	1 (3)	1
Chest pain	0	1 (3)	1
Headache	0	1 (3)	1
Hypokinesia of knee	0	1 (3)	1
Pruritus	0	1 (3)	1
Sudden sensorial verbal hearing loss	0	1 (3)	1
Bitter taste	0	1 (3)	1
Vertigo	0	1 (3)	1
Appendicitis	0	1 (3)	1
Hip pain	0	1 (3)	1
TOTAL	34	31	65

Of the 65 total events reported, 20 were regarded as treatment related. Knee pain, hypokinesia of the knee, knee swelling, and rash were considered to be treatment related adverse events. Table 4 shows the relation of the treatment related adverse events to the treatment group.

Table 4. Treatment Related Adverse Events by Treatment Group

Adverse Event	EUFLEXXA™ n = 34	Placebo n = 31
Hip pain	0	1
Hypokinesia of knee	1	0
Knee pain	10	5
Knee swelling	1	0
Rash	0	1
Taste bitter	0	1
TOTAL	12	8

CLINICAL STUDIES

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

Parameter	Number of Patients (%)	
	EUFLEXXA™	Active Control
† Kellgren and Lawrence Grading System		
Definite osteophytes (Stage 2)	88 (55.0%)	84 (52.2%)
Moderate multiple osteophytes (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)	62.7 ± 7.5 (160)	63.7 ± 7.3 (161)
Female (n)	62.9 ± 7.9 (99)	64.3 ± 7.3 (108)
Males (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 5 parameters: Age > 50 years, Stiffness < 30 minutes, Crepitus, Bony tenderness, Bony enlargement, No palpable warmth

Treatment and Evaluation Schedule

Those patients who scored an average of 41-80 mm on the five pain parameters at pre-screening were required to discontinue all non-steroid anti-inflammatory drugs (NSAIDs) and analgesics two weeks prior to entry into the trial. These patients were allowed up to 4 grams daily of acetaminophen as needed for pain relief. Patients who were eligible to participate in the study were stratified on the basis of the average pain severity (as evaluated in the pre-screening assessment) and were randomized within the center into equal treatment groups. Each treatment arm had an approximately equal number of patients with an average score of 41-60 mm and 61-80 mm. EUFLEXXA™ or the active control was administered by intra-articular injection once a week (one week apart) at Week 0, 1 and 2, for a total of three injections using aseptic technique. Effusion was aspirated if present. Follow-up evaluator assessments were conducted at Weeks 3, 6, and 12; patient self-assessments were performed at Weeks 1-3, 6 and 12. Study duration was 12 weeks.

An analysis was performed of the change in the average of patient's self-assessment of five pain parameters at Week 12 (or last visit for early dropouts) using the WOMAC on a 0-100 mm horizontal VAS. The five pain parameters are:

1. Walking on a flat surface
2. Going up and down stairs
3. Rest during the night
4. Sitting or lying
5. Standing upright

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 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

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.

Product Number: 55566-4100-1

3 disposable syringes per carton

SHELF LIFE

18 months

STORAGE INSTRUCTIONS

Store at 2°-25°C (36°-77°F). Protect from light. Do not freeze. Remove from refrigeration at least 20-30 minutes before use.

CAUTION

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

Product contact parts of the syringe contain natural rubber latex, which may cause allergic reactions.

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 mm 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 Adaptor (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.

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

MANUFACTURED FOR:

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