

PRODUCT INFORMATION

NuflexxaNuflexxa (1% Sodium hyaluronate)

CONTENT

Each 1 ml of NuflexxaNuflexxa contains:

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

DESCRIPTION

NuflexxaNuflexxa is a viscoelastic, sterile solution of highly purified, high molecular weight (2.4-3.6 million daltons) sodium hyaluronate in phosphate-buffered saline. NuflexxaNuflexxa 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 $\beta \rightarrow 1,3$ and $\beta \rightarrow 1,4$ glycosidic bonds.

INDICATION

NuflexxaNuflexxa (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 nonpharmacologic therapy and simple analgesics, e.g., acetaminophen.

CONTRAINDICATIONS

- Do not use NuflexxaNuflexxa to treat patients who have a known hypersensitivity to hyaluronate preparations.
- Do not use NuflexxaNuflexxa 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 sodium hyaluronate solutions results in formation of a precipitate. NuflexxaNuflexxa 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 may cause systemic adverse events.

PRECAUTIONS

GENERAL

- Patients having repeated exposure to NuflexxaNuflexxa 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 NuflexxaNuflexxa .
- 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 NuflexxaNuflexxa .
- 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 NuflexxaNuflexxa have not been established.

Use of Specific Populations

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

ADVERSE REACTIONS

Adverse event information regarding the use of NuflexxaNuflexxa 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 NuflexxaNuflexxa (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 NuflexxaNuflexxa 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 NuflexxaNuflexxa 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 (%)	
		NuflexxaNuflexxa (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)
	Paraesthesia	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)

n= number of patients

A total of 160 patients received 478 injections of NuflexxaNuflexxa. There were 27 reported adverse events considered to be related to NuflexxaNuflexxa 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 NuflexxaNuflexxa 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	Nuflexxa(Nuflexxa) (Number of Reports) n= 160	Commerically 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
Pruritis	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, NuflexxaNuflexxa, 24, placebo) patients were randomized into two treatment groups in a ratio of 1:1 NuflexxaNuflexxa 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 Nuflexxa 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	Nuflexxa 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
Pruritis	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	NuflexxaNuflexxa 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 NuflexxaNuflexxa 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 NuflexxaNuflexxa (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 & 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 (%)	
	Nuflexxa	Active Control
<u>* Kellgren & Lawrence Grading System</u>		
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)
<u>Osteoarthritis duration</u>		
Study knee (months prior to enrollment)	57.1 ± 45.9	60.7 ± 53.5
<u>Radiological diagnosis</u>		
Study Knee (months prior to enrollment)	3.9 ± 3.8	4.4 ± 6.4
<u>** Altman Criteria</u>		
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 (Ref. 3)-. 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., (Ref. 2)- 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. Nuflexxa Nuflexxa 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 effects of NuflexxaNuflexxa 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 score)

	Nuflexxa TM		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 Nuflexxa Nuflexxa Contains:

Sodium hyaluronate	20mg
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

Nuflexxa Nuflexxa is supplied in 2.25 ml nominal volume, disposable, pre-filled glass syringes containing 2 ml of NuflexxaTM. Only the contents of the syringe is sterile. Nuflexxa Nuflexxa is nonpyrogenic.

SHELF LIFE

3 years

STORAGE INSTRUCTIONS

Store in a cold dark place (2°-8°C; 36°-46°F). Do not freeze.

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. Remove joint effusion, if present.
2. Each package of NuflexxaNuflexxa is manufactured using aseptic filling techniques. Do not use if the blister package is opened or damaged.
3. Twenty to thirty minutes before use, remove the product box from the refrigerator, remove the blister pack from the box and allow the syringe to come to room temperature. Be sure to return any syringes not intended for use to the refrigerator.
4. Peel off the blister Tyvek backing (The syringe should be used immediately after the individual syringe blister is opened).
5. 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.**
6. 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.**
7. Apply gentle pressure to the plunger in order to expel air from the syringe needle and to verify that the syringe is operating properly.
8. The syringe is ready for use.
9. 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 NuflexxaNuflexxa.
10. For single use only. Do not resterilize.
11. Store in a cold dark place (2°-8°C; 36°-46°F). Do not freeze.
12. A dose of 2ml is injected intra-articularly into the affected knee at weekly intervals for three weeks, for a total of three injections.

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