SYNOJOYNT™
(1% sodium hyaluronate)
Product Information

CONTENT

Each prefilled syringe of SYNOJOYNT contains:

Sodium Hyaluronate	20 mg
Sodium chloride	17 mg
Disodium hydrogen phosphate, heptahydrate	0.8 mg
Sodium dihydrogen phosphate, monohydrate	0.06 mg
Water for injection	q.s.* to 2.0 mL

*q.s. = up to

DESCRIPTION

SYNOJOYNT is a sterile, non-pyrogenic, clear, viscoelastic solution of hyaluronan contained in a single-use prefilled syringe. SYNOJOYNT is a viscous solution of sodium hyaluronate in buffered physiological sodium chloride. Sodium hyaluronate is a high molecular weight fraction (approximately $2.5x10^6$ daltons) of a natural complex sugar polymer consisting of the repeating disaccharide units Na-glucuronate-N acetylglucosamine.

INDICATIONS

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

WARNINGS

- Do not concomitantly use disinfectants containing quaternary ammonium salts or chlorhexidine for skin preparations because hyaluronan can precipitate in their presence.
- Do not inject intravascularly because intravascular injections of SYNOJOYNT may cause systemic adverse events.

PRECAUTIONS

- Patients having repeated exposure to SYNOJOYNT have the potential for an immune response; however, this has not been assessed in humans.
- The safety and effectiveness of injection of SYNOJOYNT in conjunction with other intra-articular injectables, or into joints other than the knee have not been established.
- Remove any joint effusion before injecting.
- Transient pain or swelling of the injected joint may occur after intra-articular injection with SYNOJOYNT.
- The effectiveness of repeated injection cycles of SYNOJOYNT has not been established.
- The contents of the syringe must be used immediately after its packaging is opened. Do not re-sterilize the product.
- Strict aseptic administration technique must be followed.
- Do not re-use. Dispose of the syringe and any unused SYNOJOYNT after use.
- Do not use if the syringe blister package is opened or damaged.
- The route for intra-articular injection should be chosen so that damage to adjacent vital structures is avoided.
- An increase in injection pressure may indicate incorrect extra-articular placement of the needle or overfilling of the joint.
- Local anesthetics should not be used if the patient is known to be allergic or sensitive to local anesthetic.

- SYNOJOYNT™ should be used with caution in patients with pre-existing chondrocalcinosis as injection may lead to an acute attack of the condition.
- As with any viscosupplementation treatment, the patient should avoid any strenuous activities or prolonged (i.e. more than an hour) weight bearing activities within 48 hours following intra-articular injection.

USE IN SPECIFIC POPULATIONS

Pregnancy
The safety and effectiveness of SYNOJOYNT have not been established in pregnant women.

Nursing Mothers
It is not known if SYNOJOYNT is excreted in human milk. The safety and effectiveness of SYNOJOYNT have not been established in lactating women.

Children
The safety and effectiveness of SYNOJOYNT have not been demonstrated in children (21 years of age or younger).

ADVERSE REACTIONS

Adverse event information regarding the use of SYNOJOYNT as a treatment for pain in OA of the knee was available from a 26-week multicenter clinical trial conducted in the United States. This study was a three-arm prospective, randomized, double-blind, multicenter study conducted in 33 centers. Table 1 shows the summary of treatment emergent adverse events occurring in ≥1% of patients participating in this trial who received SYNOJOYNT.

Table 1
Summary of Treatment Emergent Adverse Events (TEAEs)* Occurring in ≥ 1% of Patients (Safety Analysis Population)

System Organ Class	Placebo N=197 n (%)	Euflexxa® N=199 n (%)	SYNOJOYNT N=199 n (%)	Total N=595 n (%)
Subjects with Any TEAE(s)	**76 (38.6)**	**82 (41.2)**	**76 (38.2)**	**234 (39.3)**
Gastrointestinal disorders				
Diarrhea	0	2 (1.0)	2 (1.0)	4 (0.7)
Nausea	1 (0.5)	0	2 (1.0)	3 (0.5)
General disorders and administration site conditions				
Injection site joint pain	12 (6.1)	1 (0.5)	5 (2.5)	18 (3.0)
Injection site pain	1 (0.5)	2 (1.0)	2 (1.0)	5 (0.8)
Edema peripheral	2 (1.0)	1 (0.5)	2 (1.0)	5 (0.8)
Infections and infestations				
Upper respiratory tract infections	3 (1.5)	7 (3.5)	7 (3.5)	17 (2.9)
Nasopharyngitis	8 (4.1)	3 (1.5)	5 (2.5)	16 (2.7)
Bronchitis	0	1 (0.5)	5 (2.5)	6 (1.0)
Urinary tract infection	2 (1.0)	2 (1.0)	2 (1.0)	6 (1.0)
Herpes zoster	0	0	2 (1.0)	2 (0.3)
Injury, poisoning and procedural complications				
Muscle strain	1 (0.5)	1 (0.5)	2 (1.0)	4 (0.7)
Musculoskeletal and connective tissue disorders				
Arthralgia	24 (12.2)	26 (13.1)	19 (9.5)	69 (11.6)
Joint swelling	7 (3.6)	3 (1.5)	5 (2.5)	15 (2.5)
Joint crepitation	4 (2.0)	3 (1.5)	5 (2.5)	15 (2.5)
Joint effusion	4 (2.0)	2 (1.0)	4 (2.0)	10 (1.7)
Back pain	3 (1.5)	3 (1.5)	2 (1.0)	8 (1.3)
Osteoarthritis	0	1 (0.5)	3 (1.5)	4 (0.7)
Nervous system disorders				
Headache	5 (2.5)	3 (1.5)	3 (1.5)	11 (1.8)
Sciatica	0	1 (0.5)	2 (1.0)	3 (0.5)

Respiratory, thoracic and mediastinal disorders				
Cough	0	2 (1.0)	3 (1.5)	5 (0.8)

* TEAEs were defined as those adverse events which worsened in severity on or after the date of first administration of study device or with onset date on or after date of first administration of study device.

- N/n=number of subjects
- Euflexxa® is a registered trademark of Ferring BV.

The incidence of target knee-related treatment emergent adverse events was comparable with the placebo group [32 (16.1%) subjects in the SYNOJOYNT group versus 45 (22.8%) subjects in the placebo group]. The most common target-knee related treatment-emergent adverse event, by preferred term, was arthralgia [17 (8.5%) subjects in the SYNOJOYNT group versus 21 (10.7%) subjects in the placebo group].

The incidence of device-related treatment emergent adverse events was low and comparable with the placebo group [7 (3.5%) subjects in the SYNOJOYNT group versus 11 (5.6%) subjects in the placebo group]. The most common device-related TEAE, by preferred term, was injection site joint pain [2 (1.0%) subject in the SYNOJOYNT group versus 5 (2.5%) in the placebo group].

The incidence of injection-related treatment emergent adverse events was low and comparable with the placebo group [10 (5.0%) subjects in the SYNOJOYNT group versus 12 (6.1%) subjects in the placebo group]. The most common injection-related treatment emergent adverse event, by preferred term was Injection site joint pain [3 (1.5%) subjects in the SYNOJOYNT group versus 7 (3.6%) subjects in the placebo group].

The incidence of serious adverse events (SAEs) in the SYNOJOYNT group was low and comparable with the placebo group [5 (2.5%) subjects in the SYNOJOYNT group versus 3 (1.5%) subjects in the placebo group). None of the SAEs were considered to be target-knee related, device-related or injection-related. There were no unanticipated adverse device effects in the study. There were no deaths in the study.

The incidence of TEAEs (Target-knee TEAEs, Device-related TEAEs and Injection-related TEAEs) in SYNOJOYNT was comparable with Euflexxa®.

POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Potential adverse effects (e.g., complications) associated with the use of this device and, in general, associated with intra-articular injection devices for the treatment of pain in osteoarthritis of the knee, include:

- Aggravated osteoarthritis
- Injection site reaction
- Arthralgia (knee pain)
- Localized osteoarthritis
- Arthropathy
- Joint (knee) disorder
- Arthrosis
- Joint (knee) swelling
- Baker's cyst
- Joint (knee) effusion
- Bursitis
- Joint (knee) stiffness
- Immune response
- Pain in limb
- Infection
- Paraesthesia
- Injection site erythema
- Phlebitis
- Injection site edema
- Pruritis
- Injection site pain
- Tendonitis

Incidences of rash, headache, dizziness, chills, hives, nausea, muscle cramps, peripheral edema, and malaise have also been reported in association with intra-articular injections.

A summary of the frequency and rate of adverse events identified in the clinical study for SYNOJOYNT is provided in the "Clinical Studies" section.

CLINICAL STUDIES

The safety and effectiveness of SYNOJOYNT was evaluated in a double-blind, prospective, multi-site, randomized, three-arm, parallel group, pivotal trial in adult subjects. The primary objective of the study was to evaluate the effectiveness of three weekly intra-articular doses of 2 mL of SYNOJOYNT as compared to placebo injected into the target knee for the treatment of pain in subjects with osteoarthritis. The safety and effectiveness of SYNOJOYNT was also compared with Euflexxa®.

The primary effectiveness endpoint was the change from Baseline in the Western Ontario and McMaster Universities Arthritis Index (WOMAC®) pain score in the target knee at Week 26. Secondary effectiveness endpoints were the change from Baseline in the WOMAC® pain score over time; pain, stiffness and physical function of the target knee as assessed by WOMAC® over time; and the change from Baseline in the Short Form (36) (SF-36) over time. Overall, 595 (99.3%) subjects were treated and 543 (90.7%) subjects completed the study.

Demographic and baseline characteristics for subjects participating in the study are described in Table 2 and were generally similar across treatment groups.

Table 2
Demographic and Baseline Characteristics for Study Participants [Intent-to-Treat (ITT)]

Characteristic	Placebo Group (N=199)	SYNOJOYNT Group (N=200)	Euflexxa® Group (N=200)
Age (mean ± SD)	62.0 ± 10.0	63.2 ± 9.5	63.3 ± 9.4
Sex (n, %)			
Male	89 (44.7)	79 (39.5)	83 (41.5)
Female	110 (55.3)	121 (60.5)	117 (58.5)
Target Knee (n, %)			
Right	95 (47.7)	111 (58.5)	117 (58.5)
Left	104 (52.3)	89 (44.5)	83 (41.5)
Target Knee – Tenderness (n, %)	6 (3.0)	5 (2.5)	4 (2.0)
Target Knee – Swelling (n, %)	1 (0.5)	3 (1.5)	2 (1.0)
Target Knee – Redness/Heat (n, %)	0	0	1 (0.5)
Target Knee – Effusion (n, %)	0	1 (0.5)	2 (1.0)
Target Knee Kellgren-Lawrence Grade 2 (n, %)	104 (52.3)	108 (54.0)	124 (62.0)
Target Knee Kellgren-Lawrence Grade 3 (n, %)	95 (47.7)	91 (45.5)	76 (38.0)
Target Knee Kellgren-Lawrence Grade 4 (n, %)	0	0	0
Duration for Target Knee Pain in last Month (Days; mean ± SD)	27.5 ± 4.7	27.2 ±.4.8	27.3 ± 5.1

This investigation was conducted as an adaptive investigation with two blinded interim analyses (after approximately 50% and 75% of the planned sample size), allowing for sample size reassessment as needed. No adjustments were deemed necessary after the interim analyses. The investigation was conducted over 16 months, from initiation to last subject, last visit. The investigation was considered complete (primary endpoint completion) once all subjects had completed the Week 26 follow-up visit. The duration of treatment for each subject was 3 weeks, with 23 weeks subsequent follow-up.

Study Results

Safety Results

The analysis of safety was based on the Safety Analysis Population cohort of 595 treated patients. The adverse effects and key safety outcomes for this study are presented below in Tables 6 to 10.

Overall, the incidence of Treatment-Emergent Adverse Events (TEAEs) in the SYNOJOYNT treatment group was similar to that of the saline placebo treatment group. In total, 234 (39.3%) subjects experienced 411 TEAEs: 147 TEAEs in the placebo group; 135 TEAEs in the Euflexxa® group; 129 TEAEs in the SYNOJOYNT group. In total, 9 (1.5%) subjects (3 [1.5%] subjects

placebo group; 1[0.5%] subject Euflexxa® group; 5 [2.5%] subjects SYNOJOYNT group) had a treatment-emergent serious adverse event (SAE).

There were 8 (1.3%) subjects with severe TEAEs in total. In all, there were 114 (19.2%) subjects with target knee-related TEAEs (45 [22.8%] subjects placebo group; 37 [18.6%] subjects Euflexxa® group; 32 [16.1%] subjects SYNOJOYNT group) and 31 (5.2%) subjects with any injection-related TEAEs (12 [6.1%] subjects placebo group; 9[4.5%] subject Euflexxa® group; 10[5.0%] subjects SYNOJOYNT group). There were no deaths or unexpected adverse device event (UADEs) in the study. Overall TEAEs are summarized below in Table 3.

Table 3:
Overall Summary of TEAEs – Safety Analysis Population

	Placebo N=197 n (%)	Euflexxa® N=199 n (%)	SYNOJOYNT N=199 n (%)	Total N=595 n (%)
Number of TEAE(s)[1]	147	135	129	411
Subjects with Any TEAE(s)	76 (38.6)	82 (41.2)	76 (38.2)	234 (39.3)
Subjects with Any Serious Adverse Event	3 (1.5)	1 (0.5)	5 (2.5)	9 (1.5)
Subjects with Any Severe TEAE(s)	3 (1.5)	2 (1.0)	3 (1.5)	8 (1.3)
Subjects with Any Target Knee-Related TEAE(s)	45 (22.8)	37 (18.6)	32 (16.1)	114 (19.2)
Subjects with Any Device-Related TEAE(s)	11 (5.6)	10 (5.0)	7 (3.5)	28 (4.7)
Subjects with Any Injection-Related TEAE(s)	12 (6.1)	9 (4.5)	10 (5.0)	31 (5.2)
Subjects with Any Unanticipated Adverse Device Effect	0	0	0	0
Subjects with TEAE(s) Leading to Study Discontinuation	1 (0.5)	0	4 (2.0)	5 (0.8)
Subjects with TEAE(s) Leading to Death	0	0	0	0

Note: TEAEs were those AEs which worsened in severity on or after date of first administration of study device or with onset date on or after date of first administration of study device.

Except for the number of AEs, subjects were counted only once per treatment in each row.

MedDRA V18.1 coding dictionary was used.

Abbreviation: AE(s)=adverse event(s); MedDRA=Medical Dictionary for Regulatory Activities; N/n=number of subjects; SAE=serious adverse event; TEAE(s)=treatment-emergent adverse events.

1. For each subject, multiple AEs sharing the same MedDRA preferred term were counted only once.

Overall, the most frequently experienced TEAEs (all causalities) by System Organ Class for the Safety Analysis Set were:

- Musculoskeletal and connective tissue disorders: the three most common TEAEs (all causalities) by Preferred Term (PT) were:
  - Arthralgia: 69 (11.6%) subjects (24 [12.2%] subjects placebo group; 26 [13.1%] subject Euflexxa® group; 19 [9.5%] subjects SYNOJOYNT group)
  - Joint swelling: 15 (2.5%) subjects (7 [3.6%] subjects placebo group; 3 [1.5%] subject Euflexxa® group; 5 [2.5%] subjects SYNOJOYNT group)
  - Joint crepitation: 12 (2.0%) subjects (4 [2.0%] subjects placebo group; 3 [1.5%] subject Euflexxa® group; 5 [2.5%] subjects SYNOJOYNT group)
- Infections and infestations: the three most common TEAEs (all causalities) by PT were:
  - Upper respiratory tract infection: 17 (2.9%) subjects (3 [1.5%] subjects placebo group; 7 [3.5%] subject Euflexxa® group; 7 [3.5%] subjects SYNOJOYNT group)
  - Nasopharyngitis: 16 (2.7%) subjects (8 [4.1%] subjects placebo group; 3 [1.5%] subject Euflexxa® group; 5 [2.5%] subjects SYNOJOYNT group)
  - Bronchitis: 6 (1.0%): (0 subjects placebo group; 1 [0.5%] subject Euflexxa® group; 5 [2.5%] subjects SYNOJOYNT™ group) and Urinary tract infection: 6 (1.0%): 2 (1.0%) in each treatment group
- General disorders and administration site conditions: the three most common TEAEs (all causalities) by PT were:
  - Injection site joint pain: 18 (3.0%) (12 [6.1%] subjects placebo group; 1 [0.5%] subject Euflexxa® group; 5 [2.5%] subjects SYNOJOYNT group)

- Injection site joint effusion: 8 (1.3%) (3 [1.5%] subjects placebo group; 4 [2.0%] subject Euflexxa® group; 1 [0.5%] subjects SYNOJOYNT group)
- Injection site joint swelling: 6 (1.0%) (3 [1.5%] subjects placebo group; 2 [1.0%] subject Euflexxa® group; 1 [0.5%] subjects SYNOJOYNT group)

Overall, in the SYNOJOYNT group the incidence of target knee-related TEAEs was comparable with that of the placebo group (32 [16.1%] subjects in the SYNOJOYNT group versus 45 [22.8%] subjects in the placebo group).

Target knee-related TEAEs were most commonly associated with the musculoskeletal and connective tissue disorders SOC (26 [13.2%] subjects in the placebo group, 27 [13.6%] subjects in the Euflexxa® group, 23 [11.6%] subjects in the SYNOJOYNT group) and the general disorders and administration site conditions SOC (18 [9.1%] subjects in the placebo group, 10 [5.0%] subjects in the Euflexxa® group, 9 [4.5%] subjects in the SYNOJOYNT group).

The three most common target knee-related TEAEs, by PT were arthralgia (21 [10.7%] subjects in the placebo group, 24 [12.1%] subjects in the Euflexxa® group, 17 [8.5%] subjects in the SYNOJOYNT group), injection site joint pain (12 [6.1%] subjects in the placebo group, 1 [0.5%] subjects in the Euflexxa® group, 5 [2.5%] subjects in the SYNOJOYNT group) and joint swelling (6 [3.0%] subjects in the placebo group, 2 [1.0%] subjects in the Euflexxa® group, 5 [2.5%] subjects in the SYNOJOYNT group).

Target knee-related TEAEs are summarized by SOC and PT in Table 4 below.

Table 4:
Summary of Target Knee-Related TEAEs by SOC and PT– Safety Analysis Population

System Organ Class Preferred Term	Placebo N=197 n (%)	Euflexxa® N=199 n (%)	SYNOJOYNT N=199 n (%)
Subjects with any Target Knee-Related TEAEs	45 (22.8)	37 (18.6)	32 (16.1)
General disorders and administration site conditions	18 (9.1)	10 (5.0)	9 (4.5)
Injection site bruising	1 (0.5)	0	0
Injection site erythema	0	2 (1.0)	0
Injection site haemorrhage	1 (0.5)	0	0
Injection site joint effusion	3 (1.5)	4 (2.0)	1 (0.5)
Injection site joint pain	12 (6.1)	1 (0.5)	5 (2.5)
Injection site joint swelling	3 (1.5)	2 (1.0)	1 (0.5)
Injection site joint warmth	0	2 (1.0)	0
Injection site pain	1 (0.5)	2 (1.0)	2 (1.0)
Injection site reaction	1 (0.5)	0	0
Injection site swelling	1 (0.5)	0	0
Mass	0	1 (0.5)	0
Swelling	0	0	1 (0.5)
Tenderness	0	0	1 (0.5)
Infections and infestations			
Injection site infection	0	1 (0.5)	0
Injury, poisoning and procedural complications	4 (2.0)	2 (1.0)	1 (0.5)
Contusion	1 (0.5)	0	0
Laceration	0	0	1 (0.5)
Meniscus injury	0	1 (0.5)	0
Muscle rupture	1 (0.5)	0	0
Procedural pain	0	1 (0.5)	0
Skin abrasion	1 (0.5)	1 (0.5)	0
Soft tissue injury	1 (0.5)	0	0
Musculoskeletal and connective tissue disorders	26 (13.2)	27 (13.6)	23 (11.6)
Arthralgia	21 (10.7)	24 (12.1)	17 (8.5)
Exostosis	0	2 (1.0)	0
Haemarthrosis	1 (0.5)	0	0
Joint crepitation	4 (2.0)	3 (1.5)	4 (2.0)
Joint effusion	4 (2.0)	2 (1.0)	4 (2.0)
Joint range of motion decreased	1 (0.5)	1 (0.5)	0

Joint stiffness	1 (0.5)	0	1 (0.5)
Joint swelling	6 (3.0)	2 (1.0)	5 (2.5)
Joint warmth	1 (0.5)	0	0
Osteoarthritis	0	1 (0.5)	1 (0.5)
Tendonitis	1 (0.5)	0	0
Nervous system disorders	2 (1.0)	0	0
Paraesthesia	1 (0.5)	0	0
Presyncope	1 (0.5)	0	0
Psychiatric disorders	1 (0.5)	0	0
Depression	1 (0.5)	0	0
Skin and subcutaneous tissue disorders	2 (1.0)	0	0
Erythema	2 (1.0)	0	0

Overall, in the SYNOJOYNT group the incidence of device-related TEAEs was low and comparable with the placebo group (7 [3.5%] subjects in the SYNOJOYNT group versus 11 [5.6%] subjects in the placebo group).

The three most common device-related TEAEs, by PT were injection site joint pain (5 [2.5%] subjects in the placebo group, 1 [0.5%] subjects in the Euflexxa® group, 2 [1.0%] subjects in the SYNOJOYNT group), arthralgia (2 [1.0%] subjects in the placebo group, 4 [2.0%] subjects in the Euflexxa® group, 2 [1.0%] subjects in the SYNOJOYNT group) and injection site joint effusion (2 [1.0%] subjects in the placebo group, 1 [0.5%] subjects in the Euflexxa® group, 1 [0.5%] subjects in the SYNOJOYNT group).

Device-related TEAEs by SOC and PT are summarized below in Table 5.

Table 5:
Summary of Device-Related TEAEs by SOC and PT – Safety Analysis Population

System Organ Class Preferred Term	Placebo N=197 n(%)	Euflexxa® N=197 n(%)	SYNOJOYNT N=199 n(%)
Subjects with any Device-related TEAEs	11 (5.6)	10(5.0)	7 (3.5)
General disorders and administration site conditions	8 (4.1)	5 (2.5)	4 (2.0)
Injection site erythema	0	1(0.5)	0
Injection site joint effusion	2 (1.0)	1(0.5)	1 (0.5)
Injection site joint pain	5 (2.5)	1(0.5)	2 (1.0)
Injection site joint swelling	0	2(1.0)	1 (0.5)
Injection site joint warmth	0	1(0.5)	0
Injection site pain	0	1(0.5)	1 (0.5)
Injection site reaction	1 (0.5)	0	0
Infections and infestations	0	1(0.5)	0
Injection site infection	0	1(0.5)	0
Musculoskeletal and connective tissue disorders	2 (1.0)	4(2.0)	3 (1.5)
Arthralgia	2 (1.0)	4(2.0)	2 (1.0)
Haemarthrosis	1 (0.5)	0	0
Joint effusion	1 (0.5)	0	0
Joint stiffness	1 (0.5)	0	1 (0.5)
Joint swelling	1 (0.5)	1(0.5)	0
Nervous system disorders	1 (0.5)	0	0
Presyncope	1 (0.5)	0	0
Skin and subcutaneous tissue disorders	1 (0.5)	0	0
Erythema	1 (0.5)	0	0

Note: TEAEs were those AEs which worsened in severity on or after date of first administration of study device or with onset date on or after date of first administration of study device.

MedDRA V18.1 coding dictionary was used.

Abbreviation: AE(s)=adverse event(s); MedDRA=Medical Dictionary for Regulatory Activities; N/n=number of subjects; TEAE(s)=treatment-emergent adverse events.

Primary Effectiveness Results

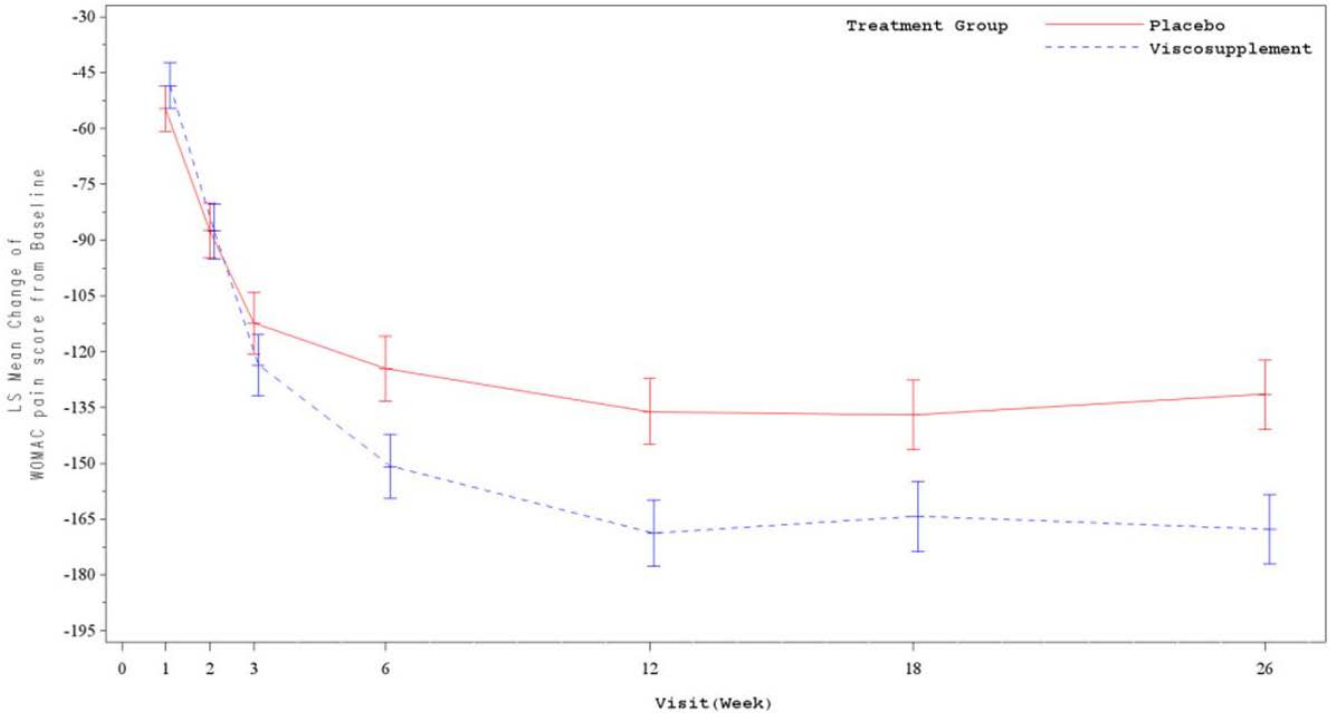
At the Week 26 visit the LSmean (standard deviation [SD]) change from Baseline in WOMAC® pain scores were -132 mm ± 128 mm in the placebo group versus -168 mm ± 129 mm in the SYNOJOYNT group (Table 6, Figure 1). At the Week 26 visit the difference (placebo versus SYNOJOYNT) in LSmean change from Baseline in WOMAC® pain score was significantly greater for the SYNOJOYNT group versus the placebo group [36 mm (95% CI: 10.25; 62.11)] demonstrating the superiority of SYNOJOYNT to placebo.

Table 6
Change in WOMAC® Pain Score from Baseline to Week 26 in Intent -to-Treat (ITT) Population

	SYNOJOYNT		Placebo		P-Value
	N	Change from baseline (mean ± SD)	N	Change from baseline (mean ± SD)	
Intent-to-Treat Population	200	-168 mm ± 129 mm	199	-132 mm ± 128 mm	0.0038

WOMAC® is a registered trademark of Nicholas Bellamy.

Figure 1
Least Squares Mean Change from Baseline in WOMAC® Pain Score – Intent-to-Treat (ITT) Population



Secondary Effectiveness Results

The following secondary effectiveness endpoints were evaluated using SYNOJOYNT, placebo and Euflexxa®:

- The change from Baseline in the WOMAC® pain score over time
- Pain, stiffness and physical function of the target knee as assessed by WOMAC® over time
- The change from Baseline in the Short Form (36) (SF-36) over time.

Over time, the mean (SD) percentage change of WOMAC® pain score from Baseline was greater for SYNOJOYNT compared with placebo. From Week 6 through Week 26 visits, the differences (placebo versus SYNOJOYNT) in LSmean change of WOMAC® pain score from Baseline were significantly larger for the SYNOJOYNT group versus the placebo group, thus demonstrating superiority of SYNOJOYNT to placebo. At Week 6, the difference (placebo versus SYNOJOYNT) in LSmean of WOMAC® pain score from Baseline was 26 mm (95% CI: 2.26; 50.39) and increased through Week 26 [36 mm (95% CI: 10.25; 62.11)].

Over time, the mean (SD) percentage change from Baseline in WOMAC® stiffness score was greater for SYNOJOYNT compared with placebo. At Week 26, for the ITT population, the mean (SD) percentage change from Baseline was higher for SYNOJOYNT [-47.37% (45.275)] compared with placebo [-35.77% (63.103)]. From Week 2 through Week 26 visits, the magnitude of LSmean change of WOMAC® stiffness score from Baseline was greater for the SYNOJOYNT group versus the placebo group and statistically significantly greater at Weeks 6, 12, and 26 (ITT population).

Over time, the mean (SD) percentage change from Baseline in WOMAC® stiffness score was similar for SYNOJOYNT compared with Euflexxa®. At Week 26, for the ITT population, the mean (SD) percentage change from Baseline was similar for SYNOJOYNT [-47.37% (45.275)] compared with Euflexxa® [-47.25% (63.020)].

At the Week 26 visit, the mean (SD) WOMAC® Physical Function Score was 659 mm (465.305) in the placebo group compared with 567 mm (467.059) in the SYNOJOYNT group, where higher WOMAC® score reflected worse physical function. At Week 26, for the ITT population, the mean (SD) percentage change from Baseline was higher for SYNOJOYNT [-48.99% (40.163)] compared with placebo [-37.37% (49.555)].

Over time, the mean (SD) percentage change from Baseline in WOMAC® Physical Function Score was similar for SYNOJOYNT compared with Euflexxa®. At Week 26, for the ITT population, the mean (SD) percentage change from Baseline was similar for SYNOJOYNT [-48.99% (40.163)] compared with Euflexxa® [-53.67% (35.781)].

LSmean increases from Baseline in SF-36 Physical Functioning, Bodily Pain, General Health, Vitality, and Role Emotional scores were observed for the SYNOJOYNT group versus the placebo group. At Week 26, LSmean increases from Baseline in SF-36 were noted for SF-36 Physical Component Summary (PCS), Mental Component Summary (MCS). The observed increases did not reach statistical significance [95% CI for the difference (placebo versusSYNOJOYNT) included 0].

At Baseline, the mean (SD) WOMAC® Physical Function Score of the target knee was 1096 mm (294.338) in the placebo group compared with 1136 mm (330.307) in the SYNOJOYNT group. At the Week 26 visit, the mean (SD) WOMAC® Physical Function Score was 659 mm (465.305) in the placebo group compared with 567 mm (467.059) in the SYNOJOYNT group, where higher WOMAC® score reflect worse physical function.

From Week 2 through Week 26 visits, the magnitude of LSmean change of WOMAC® Physical Function Score from Baseline was greater for the SYNOJOYNT group versus the placebo group and significantly greater at Weeks 6, 12, 18 and 26 (ITT population). Over time, the mean (SD) percentage change from Baseline was greater for SYNOJOYNT compared with placebo. At Week 26, for the ITT population, the mean (SD) percentage change from Baseline was higher for SYNOJOYNT [-48.99% (40.163)] compared with placebo [37.37% (49.555)].

Over time, the mean (SD) percentage change from Baseline of WOMAC® Physical Function Score was similar for SYNOJOYNT compared with Euflexxa®. At Week 26 (for the ITT population) the mean (SD) percentage change from Baseline was similar for SYNOJOYNT [-48.99% (40.163)] compared with Euflexxa® [-53.67% (35.781)].

Rescue medication use was comparable between treatment groups. From Day 1 through Week 26, the mean (SD) number of acetaminophen caplets administered was 120.6 (141.92), 108.5 (149.59) and 102.1 (124.41) for the placebo group, Euflexxa® group and SYNOJOYNT group, respectively.

HOW SUPPLIED

SYNOJOYNT is supplied in a 3 mL disposable prefilled glass syringe containing 2 mL of SYNOJOYNT. Only the contents of the syringe are sterile. Each syringe is individually sealed in a blister, and three syringe blisters are included in each carton.

This product is not made with natural rubber latex.

STORAGE INSTRUCTIONS

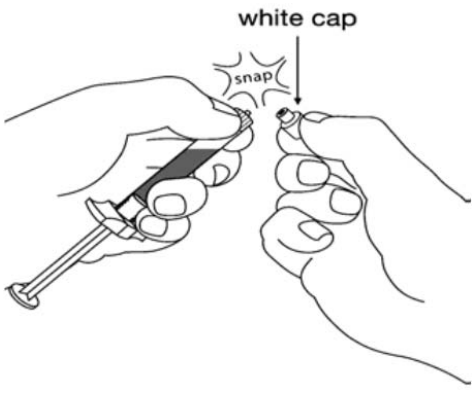
Do not use SYNOJOYNT if the package is open or damaged. Store in original package at 2°-25°C (36°-77°F). Protect from light. Do not freeze.

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

DIRECTIONS FOR USE

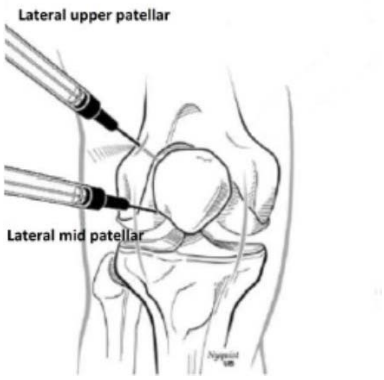
- SYNOJOYNT is a single administration preparation and should be injected into the knee joint in a series of intra- articular injections one week apart for a total of three injections.
- Carefully disinfect the injection site according to standard medical practice. Avoid using disinfectants containing quaternary ammonium salts such as benzalkonium chloride (see **WARNINGS**).
- Anesthetization of the injection site is not required; however, a topical or intra-dermal anesthetic (e.g., ethyl chloride or lidocaine) may be used at the discretion of the treating healthcare professional.
- Before initiating the preparation steps below, check if the product is damaged or broken. Do not use if the blister package is opened or damaged.
- After removal of the protective cap on the tip of the syringe (Illustration No. 1), securely attach a small gauge needle (21- or 23-gauge) to the tip. If the protective cap is damaged or there is evidence it has been opened, do not use the product.

Illustration No. 1



- Using a lateral upper patellar or lateral mid patellar approach, place needle into the joint (See Illustration 2). Ultrasound may be used to facilitate accurate needle placement of the injection. Inject SYNOJOYNT into the knee joint using strict aseptic administration technique.

Illustration No. 2



- Perform gentle aspiration to ascertain that the needle has been properly placed into the joint space.
- Remove any joint fluid.
- Over the course of 2-3 minutes, inject the full 2 mL of the syringe intra-articularly into one knee only.
- Remove syringe and needle from knee joint.
- For single use only. Do not resterilize. After administration, dispose of needle and syringe in appropriate receptacle.
- Repeat the procedure as described above at weekly intervals for three weeks, for a total of three injections.

Toll-free number for providers and patients to call with questions: 1-888-838-2872.

MANUFACTURER INFORMATION

Manufactured by:
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