INFORMATION FOR PRESCRIBERS
MONOVISC™ High Molecular Weight Hyaluronan

CAUTION:

Federal law restricts this device to sale by or on the order of a physician (or properly licensed practitioner).

DESCRIPTION:

Monovisc™ is a sterile, non-pyrogenic, viscoelastic solution of hyaluronan contained in a single-use syringe. Monovisc™ consists of high molecular weight, ultra-pure, natural hyaluronan, a complex sugar of the glycosaminoglycan family. The hyaluronan in Monovisc™ is derived from bacterial cells and is cross-linked with a proprietary cross-linker.

INDICATIONS:

Monovisc™ 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 or simple analgesics (e.g., acetaminophen).

CONTRAINDICATIONS:

- Do not administer to patients with known hypersensitivity (allergy) to hyaluronate preparations.
- Do not administer to patients with known hypersensitivity (allergy) to gram positive bacterial proteins.
- Do not inject Monovisc™ in the knees of patients with infections or skin diseases in the area of the infection site or joint.
- Do not administer to patients with known systemic bleeding disorders

WARNINGS:

- Do not concomitantly use disinfectants containing quaternary ammonium salts for skin preparation as hyaluronan can precipitate in their presence.
- Transient increases in inflammation in the injected knee following Monovisc™ injection have been reported in some patients with inflammatory osteoarthritis.

PRECAUTIONS:

General

- Strict aseptic injection technique should be used during the application of Monovisc™.
- The safety and effectiveness of the use of Monovisc™ in joints other than the knee have not been demonstrated.

- The effectiveness of Monovisc™ has not been established for more than one course of treatment.
- STERILE CONTENTS. The pre-filled syringe is intended for single use only. The contents of the syringe should be used immediately after opening. Discard any unused Monovisc™. Do not resterilize.
- Do not use Monovisc™ if the package has been opened or damaged.
- Store Monovisc™ in its original package at room temperature (below 77°F/25°C). DO NOT FREEZE.
- Remove joint effusion, if present, before injecting Monovisc™.
- Only medical professionals trained in accepted injection techniques for delivering agents into the knee joint should inject Monovisc™ for the indicated use.

Information for Patients

- Transient pain or swelling may occur after the intra-articular (IA) injection.
- As with any invasive joint procedure, it is recommended that patients avoid strenuous or prolonged (i.e., more than one hour) weight-bearing activities such as running or tennis within 48 hours following the intra-articular injection.

Use in Specific Populations

- **Pregnancy:** The safety and effectiveness of the use of Monovisc™ in pregnant women has not been tested.
- **Nursing Mothers:** It is not known if Monovisc™ is excreted in human milk. The safety and effectiveness of the use of the product in lactating women has not been tested.
- **Pediatrics:** The safety and effectiveness of the use of Monovisc™ in pediatric patients (≤ 21 years of age) has not been tested.

POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH:

Reported Device-related Adverse Events

The most common reported adverse events associated with Monovisc™ are the following:
- Arthralgia
- Joint swelling
- Injection site pain

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

A complete listing of the frequency and rate of adverse events identified in the clinical studies is provided in the Safety section.

CLINICAL STUDIES

Monovisc 0702 Pivotal Clinical Trial

Study Design:

The Monovisc 0702 study was a randomized, double-blinded, saline-controlled study conducted under IDE at 31 centers in the U.S. and Canada to evaluate the safety and effectiveness of a single injection of Monovisc™ in patients with symptomatic osteoarthritis of the knee. A total of 369 patients were enrolled. Patients were randomized in a 1:1 ratio to either Monovisc™ or saline injection. The outcome measures collected included the pain and physical function subscales from the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) Visual Analog Scale, investigator and patient global assessments and the use of rescue medication. The primary endpoint was to determine the superiority of Monovisc™ compared to saline by evaluating the proportion of patients achieving ≥ 40% relative improvement and ≥ 15mm absolute improvement from baseline in the WOMAC VAS Pain Score (100mm scale) through Week 12.

Study Population:

The patients enrolled in the study were between 35 and 75 years old and had the diagnosis of idiopathic OA based upon clinical and/or radiographic criteria of the American College of Rheumatology. Patient exclusion criteria generally included conditions or medications that could confound the assessment of pain and conditions that could be adversely affected by an intra-articular injection. A total of 369 patients were randomized to either Monovisc™ (n=184) or saline (n=185). These 369 patients comprised the Safety Population. The Intent to Treat (ITT) Population included all randomized subjects who received the study injection and had at least one follow-up visit (n=365). The Per-protocol (PP) Population included all randomized subjects who received the study injection, had at least one follow-up visit, and had no major protocol deviations (n=334). Table 1 summarizes the baseline and patient demographic characteristics for the ITT population.

Table 1. Monovisc 0702 Baseline and Patient Demographic Summary

Patient Screening Characteristics	All Patients (N=365)	MONOVISC™ (N=181)	Saline (N=184)
Age (years)			
Mean	59.2	59.7	58.7
Median	60.0	60.0	59.0
Standard Deviation	8.6	7.9	9.2
Gender [N (%)]			
Male	152 (41.6%)	74 (40.9%)	78 (42.4%)
Female	213 (58.4%)	107 (59.1%)	106 (57.6%)

Patient Screening Characteristics	All Patients (N=365)	MONOVISC™ (N=181)	Saline (N=184)
Body Mass Index (kg/m^2)			
Mean	30.1	29.8	30.4
Median	29.6	29.1	30.0
Standard Deviation	4.6	4.7	4.6
Kellgren-Lawrence (K-L) Score - Study Knee			
Grade II	200 (54.8%)	103 (56.9%)	97 (52.7%)
Grade III	165 (45.2%)	78 (43.1%)	87 (47.3%)
Baseline WOMAC Pain Score – Index Knee (mm)			
Mean	293.0	294.0	291.5
Median	291.0	296.0	288.0
Standard Deviation	60.3	60.0	60.7
Baseline WOMAC Pain Score – Contralateral Knee (mm)			
Mean	62.5	59.5	65.5
Median	54.0	44.0	60.0
Standard Deviation	48.2	48.0	48.4

Treatment and Evaluation Schedule:
Patients were followed for 26 weeks. Study visits were scheduled for screening, baseline, and weeks 2, 4, 8, 12, 20, and 26. Injections were performed aseptically at the baseline visit. Patients were required to discontinue all analgesics, including NSAIDs, for 7 days prior to the baseline visit and to accept "rescue" acetaminophen (up to a maximum of 4 grams per day) as the only medication for treatment of joint pain during the study. "Rescue" medication was not permitted within 24 hours of any study visit.

Safety Results:
Safety analyses were performed on the Safety Population, which was defined as all randomized patients. Regardless of the cause and device relatedness there were 244 (66.1%) patients that experienced adverse events for the total study cohort, where 121 (65.8%) were observed in the Monovisc™ group and 123 (66.5%) were observed in the control group. There were no significant differences between the treatment and control study groups in the frequency or type of observed adverse events.

The adverse events (AEs) most frequently reported (> 5 % in each group) and not related to the index knee were arthralgia (17.4% in the Monovisc™ group and 14.6% in the saline group); headache (13.0% in the Monovisc™ group and 15.1% in the saline group); back pain (8.7% in the Monovisc™ group and 8.6% in the saline group); pain in extremity (8.2% in the Monovisc™ group and 7.0% in the saline group); and upper respiratory tract infections (6.0% in the Monovisc™ group and 7.6% in the saline group). Adverse events considered related to the

treatment are listed in Table 2. Adverse Events were considered typical of viscosupplementation injections in this patient population and were mild or moderate in severity.

Table 2. 0702 Patients with Treatment-Related Adverse Events

AE Type	MONOVISC™ N=184	Control (Saline) N= 185
Any Adverse Event*	13 (7.1%)	10 (5.4%)
Arthralgia	7 (3.8%)	7 (3.8%)
Joint swelling	2 (1.1%)	2 (1.1%)
Joint stiffness	1 (0.5%)	2 (1.1%)
Injection site pain	3 (1.6%)	0 (0.0%)
Joint effusion	1 (0.5%)	0 (0.0%)
Pain in extremity	1 (0.5%)	0 (0.0%)
Synovitis	1 (0.5%)	0 (0.0%)
Contusion	1 (0.5%)	0 (0.0%)
Subcutaneous nodule	1 (0.5%)	0 (0.0%)
Baker's Cyst	1 (0.5%)	0 (0.0%)

* In some cases patients were involved in more than one AE

Effectiveness Results for Monovisc 0702

In the 0702 study, Monovisc™ did not demonstrate superiority over saline for the primary effectiveness endpoint of patients with ≥ 40 % relative improvement from baseline and ≥ 15 mm absolute improvement from baseline in the WOMAC VAS Pain Score through Week 12 (p=0.145).

Monovisc vs. Orthovisc Non-inferiority Analysis

A non-inferiority analysis was performed to support the effectiveness of Monovisc™ for its intended use that compared Monovisc™ with Orthovisc®, which was approved in PMA P030019 for treatment of knee pain due to osteoarthritis. Monovisc™ offers in a single injection the equivalent dose of three injections of Orthovisc®. The effectiveness of Orthovisc® for the treatment of knee pain due to osteoarthritis was demonstrated for either 3 or 4 injections of Orthovisc® using a combined data set from two randomized, controlled, double-blind multicenter IDE studies; OAK9501 and OAK2001. The combined dataset included the following groups listed in Table 3, and included a combined 3-injection Orthovisc® group (O3A1/O3) that consisted of 173 patients (83 patients from the OAK9501 study and 90 patients from the OAK2001 study). The primary non-inferiority analysis compared both the Monovisc 0702 ITT and PP populations to the Orthovisc® 3-injection groups (O3A1, O3, and the combined O3A1/O3 group).

Table 3. Orthovisc® Combined Dataset Treatment Arms

Group	Study	Description	N
O4	OAK2001	Four injections of Orthovisc	104

Group	Study	Description	N
O3	OAK9501	Three injections of Orthovisc	83
O3A1	OAK2001	Three injections of Orthovisc plus one arthrocentesis	90
O3A1/O3	OAK9501+ OAK2001	Combined group of three injections of Orthovisc	173
A4	OAK2001	Four arthrocentesis procedures (control)	100
Saline	OAK9501	Three injections of Saline (control)	81

The non-inferiority margins were set conservatively at Δ5.0mm (on a 100mm WOMAC VAS Scale), or 5% for endpoints expressed as percentages. The mean differences between treatment groups are calculated and a lower one sided 97.5% confidence interval is constructed. If the lower bound is greater than -Δ, then 'Non-inferiority' is obtained for Monovisc™ relative to the three-injection Orthovisc® group. If, in addition, the lower bound of the confidence interval is above zero, the Monovisc™ comparison is determined to be 'Non-inferior and Superior.'

Primary and secondary endpoints for the non-inferiority analysis were the same used for Orthovisc® approval. The primary endpoints were the comparison of the Proportion of Responders at the 20%, 40%, and 50% threshold levels. Secondary endpoints were the change from baseline for the WOMAC Pain Score, Pain on Standing Score, Investigator Global Assessment Score, and Patient Global Assessment Score.

Non-inferiority Analysis Results:

The mean Proportions of Responders for the primary endpoints are summarized in Table 4. For all the threshold levels, the Monovisc™ ITT or PP populations have a higher Proportion of Responders as compared to the three-injection Orthovisc® groups.

Table 4. Mean Proportion of Responders from GEE Model (Weeks 7-22)

Variable	M1 PP N=164 %, CI	M1 ITT N=181 %, CI	O3A1 N= 90 %, CI	O3 N= 83 %, CI	O3A1/O3 N=173 %, CI	O4 N= 104 %, CI	A4 N=100 %, CI	Saline N= 81 %, CI
20% Improvement in WOMAC	**74.2** (67.7, 80.7)	**72.4** (65.8,79.1)	**63.0** (52.8, 73.2)	**70.8** (60.8, 80.8)	**67.0** (52.8, 81.3)	**73.1** (64.4, 81.8)	**62.9** (53.7, 72.2)	**60.2** (49.3, 71.1)
40% Improvement in WOMAC	**61.8** (54.5, 69.0)	**58.9** (51.6, 66.2)	**50.2** (39.6, 60.7)	**54.5** (43.5, 65.4)	**52.5** (37.3, 67.7)	**63.4** (54.0, 72.9)	**48.0** (38.4, 57.6)	**41.0** (30.1, 52.0)
50% Improvement in WOMAC	**53.6** (46.2, 61.0)	**51.2** (43.8, 58.6)	**43.3** (32.9, 53.8)	**46.3** (35.4, 57.3)	**45.0** (29.9, 60.1)	**55.6** (45.9, 65.4)	**42.6** (33.2, 52.1)	**34.4** (23.8, 44.9)

Non-inferiority analyses for all endpoints were conducted using the GEE repeated measures model for weeks 7-22. The Monovisc™ ITT and PP study populations were each compared to the Orthovisc® three-injection groups (O3A1, O3, and the combined effectiveness O3A1/O3 group) for the purposes of establishing non-inferiority. Additional comparisons to the other treatment arms (O4, A4, and Saline) that were used to support the Orthovisc® PMA approval were also made.

The results of the primary endpoint analysis show that Monovisc™ (ITT or PP) is non-inferior to three injections of Orthovisc® for the O3A1 group and also for the combined O3A1/O3 group for all threshold levels. Non-inferiority was not demonstrated against the O3 group with the chosen margin.

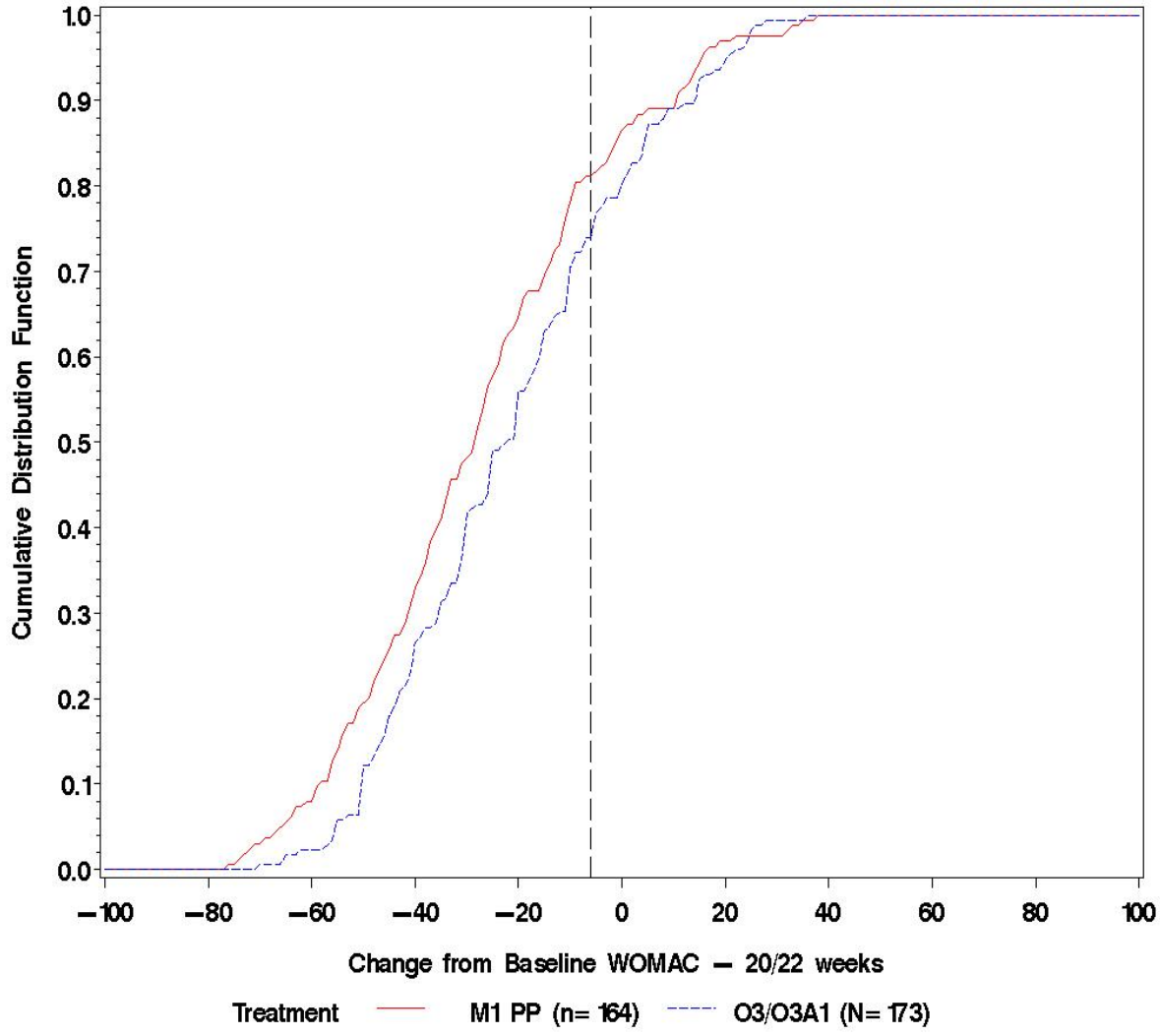
The results from the secondary endpoints show that Monovisc™ (ITT or PP) was non-inferior to the three-injection Orthovisc® groups O3 and combined O3A1/O3 for Change in WOMAC Pain Score, Pain on Standing Score, Investigator Global Score, and Patient Global Score. Monovisc™ (ITT or PP) was non-inferior to the O3A1 group for Change in WOMAC Pain Score, Investigator Global Score, and Patient Global Score (PP only).

Monovisc™ was not shown to be non-inferior to four injections of Orthovisc® (O4). The four-injection series of Orthovisc® represents a 33% increase in HA dose compared to a single injection of Monovisc™.

Monovisc™ (ITT or PP) was non-inferior or 'non-inferior and superior' against the control groups A4 and Saline for primary and secondary endpoints.

The clinical significance for the change from baseline for each of the secondary endpoints was demonstrated using Cumulative Distribution Function (CDF) plots comparing the Monovisc 0702 PP Population to the Orthovisc® three-injection combined effectiveness subgroup (O3A1/O3) at each timepoint. Figure 1 shows an example plot for the Change in WOMAC Pain Score at 20-22 weeks. The vertical dashed black line in the plot is set at the "minimum clinically important difference" (MCID). The MCID of 6.0mm was previously determined to be an acceptable difference for HA injectable products based on a meta-analysis of literature.

Figure 1. CDF Plot for Change in WOMAC Pain Score for M1 PP vs. O3A1/O3 (Weeks 20-22)



The CDF curves for the endpoints (WOMAC Pain Score, Pain on Standing Score, Investigator Global Score and Patient Global Score) show that the Monovisc™ PP population demonstrates a higher degree of clinical improvement at every timepoint relative to the Orthovisc® 3-injection combined effectiveness group (O3A1/O3).

Monovisc 0802 Repeat Injection Extension Study

Study Design and Results:

An open label study, Monovisc 0802, was conducted as an extension study of Monovisc 0702 in order to evaluate the safety of a repeat injection of Monovisc™. The extension study enrolled 240 patients, 119 of whom received a second injection of Monovisc™ and 121 of whom received an injection of Monovisc™ after receiving a saline injection during the initial treatment.

The percentage of patients experiencing AEs, regardless of cause and device relatedness, was similar for those who were previously injected with Monovisc™ (49.6%) and those previously injected with saline (45.5%). The local adverse event profile for the injected knee for those receiving a second injection of Monovisc™ was similar to the adverse event profile seen in the Monovisc 0702 study, regardless of whether patients had initially received a Monovisc™ injection or a saline injection (Table 5).

Table 5. Monovisc 0802 Adverse Events of the Injected Knee Regardless of Relatedness

Adverse Event (per patient)	Monovisc after Monovisc initial injection N=119	Monovisc after Saline initial injection N=121
Injection site erythema	0 (0.0%)	1 (0.8%)
Injection site edema	2 (1.7%)	3 (2.5%)
Injection site pain	6 (5.0%)	4 (3.3%)
Injection site reaction NOS[1]	1 (0.8%)	2 (1.7%)
Pain NOS[1]	1 (0.8%)	1 (0.8%)
Bursitis	1 (0.8%)	0 (0.0%)
Joint effusion	1 (0.8%)	1 (0.8%)
Joint stiffness	1 (0.8%)	1 (0.8%)
Joint swelling	1 (0.8%)	2 (1.7%)
Localized osteoarthritis	2 (1.7%)	1 (0.8%)

[1]NOS = Not Otherwise Specified

DETAILED DEVICE DESCRIPTION

The Monovisc™ device is a proprietary high molecular weight hyaluronic acid (HA) visco-supplementation intended for the treatment of pain in patients with moderate osteoarthritis (OA) of the knee who have failed conservative non-pharmacological therapy and simple analgesics. The device is administered by a single injection via the para-patellar approach under sterile conditions. The dosage delivered by the single injection is equivalent to three injections of Anika's FDA approved (P030019) Orthovisc HA product.

Sodium hyaluronate is a natural complex sugar of the glycosaminoglycan family. The sodium hyaluronate polymer consists of repeating disaccharide units of sodium glucuronate-N-acetylglucosamine. The molecular weight range of hyaluronic acid in Monovisc™ is between 1

and 2.9 million Daltons. Monovisc™ has a nominal sodium hyaluronate concentration of 22 mg/mL, dissolved in physiologic saline. It is supplied in a 5.0 mL syringe containing 4.0 mL of Monovisc™ The contents of the syringe are sterile, non-pyrogenic and non-inflammatory.

Monovisc™ is prepared by cross-linking hyaluronan (hyaluronic acid, HA) with proprietary cross-linking agent. The HA is derived from bacterial fermentation (*Streptococcus equi*). The HA used in Monovisc™ is the same grade and specification that is used in Orthovisc® (P030019), and delivers a comparable amount of HA to the 3-injection Orthovisc® regimen.

Each pre-filled syringe with 4 mL of Monovisc™ contains:

Hyaluronan	88 mg* (nominal)
Sodium Chloride	36 mg
Potassium Chloride	0.8 mg
Sodium Phosphate, Dibasic	4.6 mg
Potassium Phosphate, Monobasic	0.8 mg
USP water for injection	q.s. to 4 mL

*equivalent to 3 Orthovisc® injections

HOW SUPPLIED

Monovisc™ is supplied in a single-use 5 mL syringe containing a 4 mL dose of treatment. Each syringe is labeled Monovisc™ for ready identification. The contents of the syringe are sterile and non-pyrogenic. The syringe components contain no latex.

DIRECTIONS FOR USE

Monovisc™ is injected into the knee joint and is administered as a single intra-articular injection. Standard intra-articular injection site preparation and precautions should be used. Strict aseptic administration technique must be followed.

1. Using an 18 – 20 gauge needle, remove synovial fluid or effusion before injecting Monovisc™. Do not use the same syringe for removing synovial fluid and for injecting Monovisc™; however, the same 18 – 20 gauge needle should be used.

2. Remove the protective rubber cap on the tip of the syringe and securely attach a small gauge needle (18 - 20 gauge) to the tip. Twist the tip cap before pulling it off, as this will minimize product leakage.

3. To ensure a tight seal and prevent leakage during administration, secure the needle tightly while firmly holding the luer hub. Do not over tighten or apply excessive leverage when attaching the needle or removing the needle guard, as this may break the syringe tip.

4. Inject the full 4 mL in one knee only (do not overfill the joint). If treatment is bilateral, a separate syringe should be used for each knee.

MANUFACTURED BY:

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