Instructions for Use

ORTHOVISC®

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INSTRUCTIONS FOR USE
ORTHOVISC® 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:

ORTHOVISC® is a sterile, non-pyrogenic, clear, viscoelastic solution of hyaluronan contained in a single-use syringe. ORTHOVISC® consists of high molecular weight (1.0-2.9 million daltons), ultra-pure natural hyaluronan dissolved in physiological saline. Hyaluronan is a natural complex sugar of the glycosaminoglycan family. ORTHOVISC® is derived from bacterial cells.

INDICATIONS:

ORTHOVISC® is indicated in the treatment of pain in osteoarthritis (OA) of the knee in patients who have failed to respond adequately to conservative nonpharmacologic therapy and to 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 ORTHOVISC® in the knees of patients with infections or skin diseases in the area of the injection site or joint.

WARNINGS:

- Do not concomitantly use disinfectants containing quarternary ammonium salts for skin preparation as hyaluronic acid can precipitate in their presence.
- Transient increases in inflammation in the injected knee following ORTHOVISC® injection have been reported in some patients with inflammatory osteoarthritis.

PRECAUTIONS:

General

- Strict aseptic injection technique should be used during the application of ORTHOVISC®.
- The safety and effectiveness of the use of ORTHOVISC® in joints other than the knee have not been demonstrated.
- The effectiveness of a single treatment cycle of less than 3 injections has not been established. Pain relief may not be seen until after the third injection.
- The effectiveness of ORTHOVISC® 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 ORTHOVISC®. Do not resterilize.
- Do not use ORTHOVISC® if the package has been opened or damaged.
- Store ORTHOVISC® in its original package at room temperature (below 77°F/25°C). DO NOT FREEZE.
- Remove joint effusion, if present, before injecting ORTHOVISC®.
- Only medical professionals trained in accepted injection techniques for delivering agents into the knee joint should inject ORTHOVISC® 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 activity 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 ORTHOVISC® in pregnant women has not been tested.
- Nursing Mothers: It is not known if ORTHOVISC® is excreted in human milk. The safety and effectiveness of the use of the product in lactating women has not been tested.
- Children: The safety and effectiveness of the use of ORTHOVISC® in children has not been tested.

ADVERSE EVENTS:

Intra-articular injection of sodium hyaluronate preparations has occasionally been associated with allergic/anaphylactic reactions and transient hypotension, which have generally resolved spontaneously or after conservative treatment.

ORTHOVISC® was investigated in 3 randomized, controlled clinical studies conducted in the U.S. An integrated safety analysis was conducted, pooling the ORTHOVISC® groups from the 3 studies and pooling the control groups, which were either intra-articular saline injections or arthrocentesis. In the integrated analysis, there were 562 patients in the groups treated with ORTHOVISC® (434 receiving 3 injections and 128 receiving 4 injections), 296 in the group treated with physiological saline, and 123 in the group treated with arthrocentesis.

Adverse events occurring at >5% of the overall integrated population included: arthralgia (12.6% in the ORTHOVISC® group, 17.2% in the saline group, and 0.8% in the arthrocentesis group); back pain (6.9% in the ORTHOVISC® group, 12.2% in the saline group, and 4.9% in the arthrocentesis group); and headache NOS (12.1% in the ORTHOVISC® group, 16.6% in the saline group, and 17.9% in the arthrocentesis group). Injection site adverse events (including erythema, edema, pain and reaction NOS) occurred at rates of 0.4%, 0.9%, 2.5% and 0.2%, respectively, in the ORTHOVISC® group, compared to 0.0%, 0.3%, 2.0%, and 0.7% in the saline group and 0.0%, 0.0%, 0.8% and 0.8% in the arthrocentesis group. Local adverse events reported on a by-patient basis for the combined ITT populations of the three studies are presented in Table 1.

Table 1
Local individual adverse events reported on a by-patient basis for the combined ITT populations of the three studies.

Adverse Event	ORTHOVISC N = 562	Saline N = 296	Arthrocentesis N = 123
Any Adverse Event	349 (62.1%)	204 (68.9%)	65 (52.8%)
Injection site erythema	2 (0.4%)	0 (0%)	0 (0%)
Injection site edema	5 (0.9%)	1 (0.3%)	0 (0%)
Injection site pain	14 (2.5%)	6 (2.0%)	1 (0.8%)
Injection site reaction NOS[1]	1 (0.2%)	2 (0.7%)	1 (0.8%)
Pain NOS[1]	14 (2.5%)	11 (3.7%)	1 (0.8%)
Arthralgia	71 (12.6%)	51 (17.2%)	1 (0.8%)
Arthritis NOS[1]	4 (0.7%)	5 (1.7%)	0 (0%)
Arthropathy NOS[1]	5 (0.9%)	3 (1.0%)	0 (0%)
Baker's cyst	2 (0.4%)	2 (0.7%)	0 (0%)
Bursitis	6 (1.1%)	6 (2.0%)	2 (1.6%)
Joint disorder NOS[1]	2 (0.4%)	0 (0%)	0 (0%)
Joint effusion	2 (0.4%)	1 (0.3%)	1 (0.8%)
Joint stiffness	3 (0.5%)	2 (0.7%)	0 (0%)
Joint swelling	4 (0.7%)	2 (0.7%)	1 (0.8%)
Localized osteoarthritis	5 (0.9%)	1 (0.3%)	1 (0.8%)
Aggravated osteoarthritis	2 (0.4%)	0 (0%)	1 (0.8%)
Knee arthroplasty	3 (0.5%)	2 (0.7%)	0 (0%)

Notes: [1]NOS = Not otherwise specified.

Additional adverse event information was obtained from an open label study (OAK0101). The objective of the open label study was to evaluate the safety of a repeat course of intra-articular ORTHOVISC®. The patients enrolled in the open label study were previously enrolled in one of the randomized studies (OAK2001). Patients who completed OAK2001 and had persistent pain in the index knee received 3 weekly injections of ORTHOVISC® six months following the first treatment course and were followed for 6 weeks. Of 190 eligible patients, 127 had been assigned to either 4 injections of ORTHOVISC® or to 3 injections of ORTHOVISC® plus one arthrocentesis in OAK2001 and therefore underwent two courses of ORTHOVISC® treatment between the two studies. In OAK0101, adverse event profiles (type, frequency and severity of adverse events) were comparable among the three treatment groups (those who had undergone a previous series of 3 or 4 ORTHOVISC® injections and those who received only arthrocentesis in OAK2001) and were similar to those seen in the OAK2001 study and the integrated safety analysis. Table 2 compares adverse event data for patients receiving ORTHOVISC® among the integrated safety analysis ("Single Treatment"), the OAK2001 randomized study ("Single Treatment") and the OAK0101 retreatment study ("Repeat Treatment").

Table 2
Comparison of local individual adverse events reported on a by-patient basis between single and repeat treatment.

Adverse Event	ORTHOVISC Single Treatment N = 562	ORTHOVISC Single Treatment N = 247	ORTHOVISC Repeat Treatment N = 127
Any Adverse Event	349 (62.1%)	136 (55.1%)	39 (30.7%)
Injection site erythema	2 (0.4%)	2 (0.8%)	0 (0%)
Injection site edema	5 (0.9%)	1 (0.4%)	0 (0%)
Injection site pain	14 (2.5%)	3 (1.2%)	3 (2.4%)
Injection site reaction NOS[1]	1 (0.2%)	0 (0%)	4 (3.1%)
Pain NOS[1]	14 (2.5%)	3 (1.2%)	0 (0%)
Arthralgia	71 (12.6%)	20 (8.1%)	8 (6.3%)
Arthritis NOS[1]	4 (0.7%)	1 (0.4%)	0 (0%)
Arthropathy NOS[1]	5 (0.9%)	0 (0%)	0 (0%)
Baker's cyst	2 (0.4%)	0 (0%)	0 (0%)
Bursitis	6 (1.1%)	2 (0.8%)	0 (0%)
Joint disorder NOS[1]	2 (0.4%)	0 (0%)	0 (0%)
Joint effusion	2 (0.4%)	2 (0.8%)	1 (0.8%)
Joint stiffness	3 (0.5%)	0 (0%)	0 (0%)
Joint swelling	4 (0.7%)	2 (0.8%)	2 (1.6%)
Localized osteoarthritis	5 (0.9%)	3 (1.2%)	1 (0.8%)
Aggravated osteoarthritis	2 (0.4%)	2 (0.8%)	0 (0%)
Knee arthroplasty	3 (0.5%)	0 (0%)	0 (0%)

CLINICAL STUDIES

The effectiveness of ORTHOVISC® for the treatment of osteoarthritis of the knee was evaluated in three main studies; two randomized, controlled, double-blind multicenter studies (OAK9501 and OAK2001) that involved unilateral treatment, and one study (OAK9801) that involved bilateral treatment. Because bilateral treatment confounded the assessment of effectiveness of the OAK9801 study, the effectiveness data are summarized for the OAK9501 and OAK2001 studies. Safety data for all three studies are reported in "Adverse Events."

Study Design/Analysis

The objective of the randomized studies was to assess the effectiveness of ORTHOVISC® for the treatment of joint pain of patients with idiopathic osteoarthritis of the knee. The OAK9501 study randomized patients to 3 weekly injections of either ORTHOVISC® (O3) or saline. The OAK2001 study randomized patients to one of three treatments: 4 ORTHOVISC® injections (O4), 3 ORTHOVISC® injections + 1 arthrocentesis (O3A1) procedure, or 4 arthrocentesis (A4) procedures. Follow-up occurred at weeks 7/8, 11/12, 15/16 and 21/22, with final follow-up at week 27/28. When each study was analyzed individually, the primary analyses for each study did not show statistical significance. A combined analysis was additionally performed. The combined data consisted of data obtained from a subgroup of patients from each of the studies (the "ITT Subgroup" from OAK9501 and the "Evaluable Subgroup" from OAK2001) who had Kellgren-Lawrence radiographic grades of II or III at baseline and WOMAC pain in the contralateral knee of <175mm (out of 500) and is referred to as the effectiveness subgroup population. For the effectiveness subgroup population, the primary effectiveness analysis performed was to determine the proportion of patients achieving a 20% improvement from baseline in the WOMAC Pain Score in conjunction with a minimum absolute improvement of 50 mm from baseline in the WOMAC Pain Score, and a 40% and 50% improvement from baseline in WOMAC Pain Score at four assessment points between Weeks 7/8 to 21/22 for the index knee.

Study Population

OAK9501 included 226 patients at 10 centers, and OAK2001 involved 373 patients at 24 centers. Within the individual studies, baseline and demographic variables were similar among groups. Table 3 below summarizes the baseline and patient demographic characteristics for the combined effectiveness subgroup.

Table 3
Baseline and patient demographics summary—effectiveness subgroup.[1]

Characteristic	O3 N = 83	Saline x 3 N = 81	O4 N = 104	O3A1 N = 90	A4 N = 100
No. (%) female	51 (61.4%)	49 (60.5%)	46 (44.2%)	59 (65.5%)	50 (50.0%)
Mean ±SD age (years)	65 ± 8	68 ± 9	59 ± 9	59 ± 9	59 ± 8
Mean ±SD BMI (kg/m^2)	32 ± 7	30 ± 6	29 ± 4	30 ± 4	30 ± 4
Mean ±SD WOMAC Pain (0-500mm) Study Knee	274 ± 65	268 ± 70	288 ± 60	290 ± 50	293 ± 59
Mean ±SD WOMAC Pain (0-500mm) Contralateral	83 ± 57	87 ± 54	69 ± 47	70 ± 47	68 ± 48
Mean ±SD Investigator Global (0-100mm)	53 ± 19	51 ± 19	59 ± 14	58 ± 14	58 ± 15
Mean ±SD Patient Global (0-100mm)	56 ± 20	53 ± 22	67 ± 15	62 ± 17	64 ± 15

Notes: [1]Patients with Kellgren-Lawrence radiographic grades of II or III at baseline and WOMAC pain in the contralateral knee of <175mm (out of 500).

Combined Study Results
In the combined analysis of OAK9501 and OAK2001, two subgroup populations (representing patients with baseline Kellgren-Lawrence grade II or III radiographic findings and contralateral knee pain <175 mm on the WOMAC Pain Score) were analyzed together, comprising 5 treatment groups (4 ORTHOVISC® injections [O4], 3 ORTHOVISC® injections followed by 1 arthrocentesis [O3A1], 3 ORTHOVISC® injections [O3], 4 arthrocentesis procedures [A4] and 3 saline injections [Saline]). For the GEE analyses, the O3A1 and O3 groups were also pooled to form a sixth group [O3A1/O3].

The primary effectiveness analysis was performed to determine the proportion of patients achieving a 20% improvement from baseline in the WOMAC Pain Score in conjunction with a minimum absolute improvement of 50 mm from baseline in the WOMAC Pain Score, and a 40% and 50% improvement from baseline in WOMAC Pain Score at four assessment points between Weeks 7/8 to 21/22 for the index knee. A significantly larger proportion of O4 patients achieved 40% and 50% improvements from baseline in WOMAC Pain Score compared to both A4 and Saline over 7-22 weeks (based on GEE analysis). Similarly, a significantly larger proportion of O3 and O3A1/O3 patients achieved 40% and 50% improvements from baseline in WOMAC Pain Score than Saline patients (based on GEE analysis) (Table 4). Table 5 presents the mean number of patients from the effectiveness subgroup over the four follow-up visits that achieved improvement over weeks 7 through 22.

Table 4
GEE Results (P-Values) for the Effectiveness Subgroups for the Primary Endpoints

Endpoint	O4 vs. A4	O4 vs. Saline	O3 vs. Saline
≥ 20% improvement from baseline and 50 mm absolute improvement in WOMAC Pain	0.0738	0.1116	0.0789
≥ 40% improvement in WOMAC Pain Score from baseline	**0.0094***	**0.0015***	**0.0166***
≥ 50% improvement in WOMAC Pain Score from baseline	**0.0360***	**0.0015***	**0.0274***

O4 4 weekly ORTHOVISC® injections—OAK2001 Study
O3 3 weekly ORTHOVISC® injections—OAK9501 Study
A4 4 control [arthrocentesis only] procedures—OAK2001 Study
Saline 3 control [saline injection] procedures—OAK9501 Study
* Statistically significant

Table 5
Summary of mean number patients achieving primary individual patient success criteria—effectiveness subgroups from OAK9501 and OAK2001—over weeks 7 through 22 (4 visits).

Endpoint	O4 N = 104	O3A1 N = 90	A4 N = 100	O3 N = 83	Saline x 3 N = 81
Mean No. (%) patients achieving ≥20% improvement from baseline and absolute improvement of 50 mm in WOMAC Pain	77.5 (74.5%)	58.3 (64.7%)	64.5 (64.5%)	59.3 (71.4%)	50.8 (62.7%)
Mean No. (%) patients achieving ≥40% improvement from baseline in WOMAC Pain	68.0 (65.4%)	47.0 (52.2%)	48.8 (48.8%)	45.8 (55.1%)	34.3 (42.3%)
Mean No. (%) patients achieving ≥50% improvement from baseline in WOMAC Pain	59.3 (57.0%)	40.5 (45.0%)	43.5 (43.5%)	38.5 (46.4%)	28.3 (34.9%)

O4 4 weekly ORTHOVISC® injections—OAK2001 Study
O3A1 3 weekly ORTHOVISC® injections + 1 control [arthrocentesis only] procedure—OAK2001 Study
O3 3 weekly ORTHOVISC® injections—OAK9501 Study
A4 4 control [arthrocentesis only] procedures—OAK2001 Study
Saline 3 control [saline injection] procedures—OAK9501 Study

Summary
In summary, with respect to patients achieving ≥40% and ≥50% improvement in WOMAC Pain Score compared to baseline, the four injection ORTHOVISC® regimen demonstrated effectiveness compared to both Saline and Arthrocentesis control procedures, and the three-weekly injection regimen demonstrated effectiveness compared to Saline in the indicated patient population.

DETAILED DEVICE DESCRIPTION

Hyaluronan is a high molecular weight polysaccharide composed of repeating disaccharide units of sodium glucuronate and N-acetylglucosamine.

Each syringe contains the following in a 2 mL dose sterile-filled into a syringe:

Hyaluronan	30 mg
Sodium Chloride	18 mg
Water for Injection	q.s. up to 2.0 mL

ORTHOVISC® does not contain any synthetic additives.

HOW SUPPLIED

ORTHOVISC® is supplied as a sterile-filled solution, in a single-use syringe, sealed in a pouch inside a carton. The product is presented as a sterile, non-pyrogenic solution in a 3 mL syringe. Each syringe is labeled “ORTHOVISC®” for ready identification. A rubber cap is provided on the syringe tip to prevent leakage and protect sterility of the product. The ORTHOVISC® syringe components contain no latex.

DIRECTIONS FOR USE

ORTHOVISC® is injected into the knee joint in a series of intra-articular injections one week apart for a total of three or four injections. Standard intraarticular injection site preparation, aseptic technique and precautions should be used. Do not concomitantly use disinfectants containing quaternary ammonium salts for skin preparation as hyaluronic acid can precipitate in their presence.

- After removal of the protective rubber cap on the tip of the syringe, securely attach a small gauge needle (18-21 gauge) to the tip.
- Inject ORTHOVISC® into the knee joint using proper injection technique.
- Inject the full contents of the syringe into one knee only.
- If treatment is bilateral, a separate syringe should be used for each knee.
- If symptoms return, repeat courses of ORTHOVISC® may be administered.

ORTHOVISC® is a registered trademark of Anika Therapeutics, Inc.

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Patient Information
ORTHOVISC® High Molecular Weight Hyaluronan

What is ORTHOVISC®?

ORTHOVISC® is a viscous (thick) sterile mixture made from highly purified hyaluronan from bacterial fermentation. Hyaluronan is a natural chemical found in the body. High amounts of hyaluronan are found in the 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 work properly. When you have osteoarthritis, there may not be enough natural hyaluronan in the joint, and the quality of that hyaluronan may be poorer than normal. ORTHOVISC® is given in a shot (injection) directly into the knee joint.

What is ORTHOVISC® used for?

ORTHOVISC® is used to relieve knee pain due to osteoarthritis. It is used for patients who do not get adequate pain relief from simple pain relievers like acetaminophen or from exercise and physical therapy.

What are the benefits of ORTHOVISC®?

Clinical trials conducted in the U.S. have shown that ORTHOVISC® provides pain relief to patients who have not been able to find pain relief with simple pain medication or exercise compared to saline placebo injections.

What other treatments are available for osteoarthritis?

If you have pain due to osteoarthritis of the knee, there are things you can do that do not involve ORTHOVISC® injections. These include:

Non-drug treatments:
- Avoiding activities that cause pain in your knee
- Exercise
- Physical therapy
- Removal of excess fluid from the knee

Drug therapy:
- Pain medication such as acetaminophen and narcotics
- 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 knee joint

Are there any reasons why you should not take ORTHOVISC®?

- You should not take this product if you are allergic to hyaluronate products.
- If you have any known allergies, you should consult with your healthcare professional to determine if you are able to take ORTHOVISC®.
- You should not have an injection into the knee if you have infections or skin diseases around the injection site.

Things you should know about ORTHOVISC®

- ORTHOVISC® should be injected by a qualified physician or properly licensed practitioner.
- Tell your healthcare professional if you have any known allergies before ORTHOVISC® is administered.
- For 48 hours after you receive the injection, you should avoid activities such as jogging, tennis, heavy lifting or
- standing on your feet for a long time (more than one hour).
- The safety and effectiveness of ORTHOVISC® in joints other than the knee has not been demonstrated in U.S. studies.
- The safety and effectiveness of ORTHOVISC® has not been shown in pregnant or nursing women. You should tell your healthcare professional if you are pregnant or nursing.
- The safety and effectiveness of ORTHOVISC® has not been shown in children.
- The effectiveness of ORTHOVISC® has not been established for more than one course of treatment.

Possible complications

- Side effects are sometimes seen when ORTHOVISC® is injected into the knee joint. These can include: pain, swelling, heat, rash, itching, bruising and/or redness. You may also feel achy. These reactions are generally mild and do not last long.

- If any of these symptoms or signs appear after you are given ORTHOVISC® or if you have any other problems, you should call your healthcare professional.

How is ORTHOVISC® given?

Your healthcare professional will inject ORTHOVISC® (30 mg/2 mL) into your knee once a week, for a total of 3 or 4 injections.

DePuy Mitek
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