A NATURAL BALANCE BETWEEN SCIENCE AND NATURE.
ORTHOVISC®: CLOSE TO NATURE.
High Molecular Weight Hyaluronan

ORTHOVISC: Closely matches healthy synovial fluid.

Properties of synovial fluid:
- Molecular weight (million daltons)
- Elasticity (Pa at 2.5 Hz)
- Viscosity (Pa at 2.5 Hz)

ORTHOVISC® High Molecular Weight Hyaluronan has the highest concentration of hyaluronic acid (HA) amongst available viscosupplements.

Hyaluronic acid concentration – mg/mL

<table>
<thead>
<tr>
<th>Viscosupplement</th>
<th>Concentration (mg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Synvisc®</td>
<td>8</td>
</tr>
<tr>
<td>Synvisc-ONE®</td>
<td>10</td>
</tr>
<tr>
<td>Gel-One®</td>
<td>10</td>
</tr>
<tr>
<td>Hyalgan®</td>
<td>10</td>
</tr>
<tr>
<td>Supartz®</td>
<td>10</td>
</tr>
<tr>
<td>EuFlexxa®</td>
<td>15</td>
</tr>
</tbody>
</table>

High concentration of HA in synovial fluid (SF) is essential for normal joint function:
- Responsible for shock absorbing and lubricating properties of SF, which are diminished by osteoarthritis
- Reduces wear and attrition of cartilage
- May be important for nutrition of cartilage
- May eliminate metabolites and unhealthy substances from joint cavity
High purity may minimize risk of inflammatory reactions.\textsuperscript{11,12}

- ORTHOVISC contains no additives
- Derived from bacterial cells, it can be prescribed to patients with known avian allergies
- Repeat courses may be safely administered\textsuperscript{3}

Comparison of syringe contents

<table>
<thead>
<tr>
<th>Syringe</th>
<th>Hyaluronan (mg)</th>
<th>Sodium chloride (mg)</th>
<th>Additives</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORTHOVISC 2 mL</td>
<td>30</td>
<td>18</td>
<td>No additives</td>
</tr>
<tr>
<td>SYNVISC\textsuperscript{®} 2 mL</td>
<td>Hylan polymers (hyal A + hyal B) 16</td>
<td>17</td>
<td>0.32 mg Disodium hydrogen phosphate, 0.08 mg Sodium dihydrogen phosphate monohydrate</td>
</tr>
<tr>
<td>SYNVISC-ONE\textsuperscript{®} 6 mL*</td>
<td>Sodium hyaluronate 20</td>
<td>17</td>
<td>0.1 mg Monobasic sodium phosphate, 1.2 mg Dibasic sodium phosphate</td>
</tr>
<tr>
<td>HYALGAN\textsuperscript{®} 2 mL</td>
<td>Sodium hyaluronate 20</td>
<td>17</td>
<td>1.34 mg Dibasic sodium phosphate dodecahydrate, 0.04 mg Sodium dihydrogen phosphate dihydrate</td>
</tr>
<tr>
<td>SUPARTZ\textsuperscript{®} 2.5 mL</td>
<td>Sodium hyaluronate 25</td>
<td>21.25</td>
<td>1.12 mg Disodium hydrogen phosphate dodecahydrate, 0.1 mg Sodium dihydrogen phosphate dihydrate</td>
</tr>
<tr>
<td>EUFLEXXA\textsuperscript{TM} 2 mL</td>
<td>Sodium hyaluronate 20</td>
<td>17</td>
<td>1.12 mg Disodium hydrogen phosphate dodecahydrate, 1.93 mg Sodium dihydrogen phosphate dihydrate</td>
</tr>
<tr>
<td>GEL-ONE\textsuperscript{®} 3 mL</td>
<td>Cross linked hyaluronate 30</td>
<td>24.3</td>
<td>0.89 mg Dibasic sodium phosphate dodecahydrate</td>
</tr>
</tbody>
</table>

*SYNVISC-ONE\textsuperscript{®} 6 mL = 3 times content of SYNVISC\textsuperscript{®} 2 mL.

Visual depiction of content not to scale. Illustrations for presentation purposes only.
ORTHOVISC: EFFICACY THAT MATCHES EXPECTATION.

Proven efficacy across 26 weeks of randomized controlled trials.\textsuperscript{3,13}

- ORTHOVISC provided significant improvement in WOMAC pain score versus saline
- Up to 6 months of symptom relief with 3 or 4 injections

Significant improvement in WOMAC pain score (effectiveness population\textsuperscript{1})\textsuperscript{13}

*Statistically significant difference between treatment groups (\textit{P}<0.05 vs. control group).
\textsuperscript{1}Patients with contralateral WOMAC knee pain score less than 12.

- 58\% of patients achieved 5 units or greater improvement in mean pain score (control = 40\%)\textsuperscript{13}
- Twice as many achieved 7 units or greater improvement (ORTHOVISC 30\% vs. control 17\%)\textsuperscript{13}
Don’t wait until it’s too late for a nonsurgical option.

### Pain Scale

<table>
<thead>
<tr>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild Pain</td>
<td>Moderate Pain</td>
<td>Severe Pain</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

- Diagnose and treat early for improved results\(^1\)
- ORTHOVISC demonstrated statistically and clinically significant symptom improvement when used in patients with mild to moderate knee osteoarthritis\(^{13}\)

\(^1\)Kellgren-Lawrence Grade II or III radiographic evidence of knee osteoarthritis, WOMAC Osteoarthritis Index pain score of 13 or greater (possible range, 5-25).
ORTHOVISC® High Molecular Weight Hyaluronic Acid

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

DESCRIPTION
ORTHOVISC® is a sterile, non-pyrogenic, clear, viscosoluble solution of hyaluronan contained in a single-use syringe. ORTHOVISC® consists of high molecular weight (1.0-2.9 million daltons), ultra-pure natural hyaluronic acid 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 hyaluronan 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 at 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 CONCENTRATES. The pre-filled syringe is intended for single use only. The content of the syringe should be used immediately after opening. Discard any unused ORTHOVISC®. Do not re-stereilize.
• 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 (AIA) injection.
• As with any invasive 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
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; 12.4% in the saline group, and 0.4% in the arthrocentesis group); headache NOS (0.8% in the ORTHOVISC® group, 0.8% in the saline group, and 1.4% 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%, 0.0%, and 0.7% in the saline group and 0.0%, 0.0%, 0.0% and 9.8% 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.

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 (OAK501 and OAK001) that evaluated the treatment, and one study (OAK001) that involved bilateral treatment. Because bilateral treatment confounded the assessment of effectiveness of the OAK5001 study, the effectiveness data are summarized for the OAK5001 and OAK001 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 OAK5001 study randomized patients to 3 weekly injections of either ORTHOVISC® (O3) or saline. The OAK001 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 analysis for each study did not show statistical significance. A combined analysis was additionally performed. The combined analysis consisted of data obtained from a subgroup of patients from each of the studies (“the ITT Subgroup”) from OAK5001 and the “Evaluative Subgroup” from OAK001 who had Kellgren-Lawrence radiographic grades of 0 or II at baseline and WOMAC pain in the contralateral knee of <175 mm (out of 500) and is referred to as the WOMAC 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 conformation 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
OAK5001 included 229 patients at 10 centers, and OAK001 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.

COMBINED STUDY RESULTS
In the combined analysis of OAK5001 and OAK001, 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],...
ORTHOVISC® High Molecular Weight Hyaluronan

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 compared to both A4 and 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

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>O4 vs. A4</th>
<th>O4 vs. Saline</th>
<th>O3 vs. Saline</th>
</tr>
</thead>
<tbody>
<tr>
<td>20% improvement from baseline and 50 mm absolute improvement in WOMAC Pain</td>
<td>0.0738</td>
<td>0.1116</td>
<td>0.0789</td>
</tr>
<tr>
<td>40% improvement in WOMAC Pain Score from baseline</td>
<td>0.0094*</td>
<td>0.0015*</td>
<td>0.0166*</td>
</tr>
<tr>
<td>50% improvement in WOMAC Pain Score from baseline</td>
<td>0.0360*</td>
<td>0.0015*</td>
<td>0.0274*</td>
</tr>
</tbody>
</table>

Table 5

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

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.

**DIRECTIONS FOR USE**

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

**HOW SUPPLIED**

ORTHOVISC® is supplied as a sterile-filled solution, in a single-use syringe, sealed in a sterile 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.

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 intra-articular injection site preparation, aseptic technique and precautions should be used. Do not concomitantly use disinfectants containing quarternary 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.

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**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:
- Hyaluronic Acid 30 mg
- Sodium Chloride 18 mg
- Water for Injection qs. up to 2.0 mL

ORTHOVISC® does not contain any synthetic additives.

**MANUFACTURED BY**

Anika Therapeutics, Inc.
236 West Cummings Park
Woburn, MA USA 01801

**PRODUCT CODE: 277500**

DePuy Synthes Mitek Sports Medicine
325 Paramount Drive
Raynham, MA 02767

NDC code: 59676-0360-01
Product Code: 277500

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MATCH WHAT EXISTS.

It’s only natural.

- Only non-avian HA with proven efficacy up to 6 months
- Highest HA concentration among viscosupplements
- Closely matches healthy synovial fluid
- Provides improvement in WOMAC pain score versus saline at all time points
- Up to 6 months of symptom relief with 3 or 4 injections

Don’t wait, treat early.

For additional information, please call your Mitek Sports Medicine Sales Consultant at 1-800-382-4682 or visit us at www.orthovisc.com.


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ORTHOVISC® is a registered trademark of Anika Therapeutics.

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