SYNVISC® Rx Only
HYLAN G-F 20

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

DESCRIPTION
SYNVISC® (hyaluronan)(Hylan G-F 20) is an elastoviscous high molecular weight fluid containing hyaluron A and hyalin B polymers produced from chicken combs. Hyaluron derivatives of hyaluronan (sodium hyaluronate). Hylan G-F 20 is unique in that the hyaluronan is chemically crosslinked. Hyaluronan is a long-chain polymer containing repeating disaccharide units of Na-glucuronate-N-acetylglucosamine.

INDICATIONS
SYNVISC 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 administer to patients with known hypersensitivity (allergy) to hyaluronan (sodium hyaluronate) preparations.
Do not inject SYNVISC in the knees of patients having knee joint infections or skin diseases or infections in the area of the injection site.

WARNINGS
Do not concomitantly use disinfectants containing quaternary ammonium salts for skin preparation because hyaluronan can precipitate in their presence.
Do not inject SYNVISC extra-articularly or into the synovial tissues and capsule. Local and systemic adverse events, generally in the area of the injection, have occurred following extra-articular injection of SYNVISC.

Intravascular injections of SYNVISC may cause systemic adverse events. Some cases of skin necrosis have been reported after intra-articular use of hyaluronic acid. Patients should be instructed to contact their treating physician if signs of skin disorder (such as change of color or open sores) appear.

PRECAUTIONS
General
The effectiveness of a single treatment cycle of less than three injections (2 mL each) of SYNVISC has not been established.
The safety and effectiveness of SYNVISC in locations other than the knee and for conditions other than osteoarthritis have not been established.
The safety and effectiveness of the use of SYNVISC concomitantly with other intra-articular injectables have not been established.
Use caution when injecting SYNVISC into patients who are allergic to avian proteins, feathers, and egg products.
The safety and effectiveness of SYNVISC in severely inflamed knee joints have not been established.
Strict aseptic administration technique must be followed.
STERILE CONTENTS. The syringe is intended for single use. The contents of the syringe must be used immediately after its packaging is opened. Discard any unused SYNVISC.
Do not use SYNVISC package is opened or damaged. Store in original packaging (protected from light) at room temperature below 86°F (30°C). DO NOT FREEZE.
Remove synovial fluid or effusion before each SYNVISC injection.
SYNVISC should be used with caution when there is evidence of lymphatic or venous stasis in the leg to be injected.

Information for Patients
Provide patients with a copy of the Patient Labeling prior to use.
Transient pain, swelling and/or effusion of the injected joint may occur after intra-articular injection of SYNVISC. In some cases the effusion may be considerable and can cause pronounced pain; cases where swelling is extensive should be discussed with the physician.
As with any invasive joint procedure, it is recommended that the patient avoid any strenuous activities (for example, high-impact sports such as soccer, tennis or jogging) or prolonged weight-bearing activities for approximately 48 hours following the intra-articular injection. The patient should consult his or her physician regarding the appropriate time to resume such activities.

Use in Specific Populations
Pregnancy: The safety and effectiveness of SYNVISC have not been established in pregnant women.
Nursing mothers: It is not known if SYNVISC is excreted in human milk. The safety and effectiveness of SYNVISC have not been established in lactating women.
Pediatrics: The safety and effectiveness of SYNVISC have not been established in pediatric patients. Pediatric patients are defined as patients ≤ 21 years of age.

POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Reported Device-Related Adverse Events
The most commonly reported adverse events associated with SYNVISC are the following:
- Pain in the injected knee
- Swelling in the injected knee
- Joint effusion

Potential Adverse Events
The following adverse events are among those that may occur in association with intra-articular injections, including SYNVISC:
- Arthralgia
- Joint stiffness
- Joint effusion
- Joint swelling
- Joint warmth
- Injection site pain
- Arthritis
- Arthropathy
- Gait disturbance

A summary of adverse events identified in the clinical studies is provided in the Adverse Event Section below.

Post-marketing Experience
SYNVISC® (3-injection regimen) post-marketing experience has identified the following systemic events to occur rarely with administration: rash, hives, itching, fever, nausea, headache, dizziness, chills, muscle cramps, parasthesia, peripheral edema, malaise, respiratory difficulties, flushing and facial swelling. There have been rare reports of thrombocytopenia coincident with SYNVISC (3-injection regimen) injection.

Hypersensitivity reactions including anaphylactic reaction, anaphylactoid reaction, anaphylactic shock and angioedema have been reported.

Adverse Events Involving the Injected Joint
Clinical Trials
A total of 511 patients (559 knees) received 1771 injections in seven clinical trials of SYNVISC. There were 922 patients in 37% of patients injected in 22% of patients injected and after swelling after these injections. Ten patients (10 knees) were treated with arthrocentesis and removal of joint effusion.

Two additional patients (two knees) treated with intra-articular steroids. Two patients (two knees) received NSAIDs. One of these patients also received arthrocentesis. One patient was treated with arthroscopy.

Fifteen patients with adverse events localized to the knee were left to receive no further treatment or only analogues.

A total of 157 patients have received 553 injections in the three clinical trials of repeated courses of SYNVISC treatment. The reports in these trials describe a total of 48 reports of adverse events localized to the injected knee in 35 patients (22% of patients) that occurred after injections in these patients during their second course of treatment. These adverse events accounted for 6.3% of injections in 22.3% of patients as compared to 2.2% of injections in 7.2% of patients in a single course of SYNVISC injections. In addition, reports of two retrospective studies during the post-marketing period have described adverse effects localized to the injected knee that have occurred after 4.4% and 8.3% of injections that patients had received during one or more repeated courses of SYNVISC treatment.

Postmarket Experience
The most common adverse events reported have been pain, swelling and/or injection in the injected knee. Cases of acute inflammation, characterized by joint pain, swelling, effusion and sometimes joint warmth and/or stiffness, have been reported following intra-articular injection of SYNVISC. Analysis of synovial fluid reveals aseptic fluid with no crystals. This reaction often responds within a few days to treatment with Non Steroidal Anti Inflammatory Drugs (NSAIDS), intra-articular steroids and/or arthrocentesis.

Rarity, arthroscopy has been performed. The occurrence of post-injection effusion may be associated with patient history of effusion, advanced stage of disease and/or the number of injections or treatment courses a patient receives. Reactions generally abate within a few days. Clinical benefit from the treatment may still occur after such reactions.

The clinical trials described above included 28 patients who received a second course of SYNVISC injections (132 injections). There were twelve reports in nine patients (9.1% of injections, 23.7% of patients) of knee pain and/or swelling after these injections. Reports of two additional clinical trials in which patients received repeated courses of SYNVISC treatment have been described during the post-marketing period. One of these trials included 24 patients who received 210 injections during a second course of SYNVISC treatment; the other contained 71 patients who received 211 injections during a second course of SYNVISC treatment. Intra-articular infections did not occur in any of the clinical trials and have been reported only rarely during clinical use of SYNVISC.

Other Adverse Events
Clinical Trials
In the three concurrently controlled clinical trials with a total of 112 patients who received SYNVISC and 110 patients who received either saline or arthrocentesis, there were no statistically significant differences in the numbers or types of adverse events between the group of patients that received SYNVISC and the group that received control treatments.

Systemic adverse events each occurred in 10 (2.0%) of the SYNVISC treated patients. There was one case each of rash (thorax and back) and itching of the skin following SYNVISC injections in these studies. These symptoms did not recur when these patients received additional SYNVISC injections. The remaining generalized adverse events reported were calf cramps, hemorrhoid problems, ankle pain, muscle pain, tonsillitis with nausea, tachyarythmia, phlebitis with varicosities and low back pain.

Postmarket Experience
Other adverse events reported include: rash, hives, itching, fever, nausea, headache, dizziness, chills, muscle cramps, parasthesia, peripheral edema, malaise, respiratory difficulties, flushing and facial swelling. There have been rare reports of thrombocytopenia coincident with SYNVISC injection. These medical events occurred under circumstances where causal relationship to SYNVISC is uncertain. (Adverse events reported only in worldwide postmarketing experience, not seen in clinical trials, are considered more rare and are italicized.)

CLINICAL STUDIES
The safety and effectiveness of SYNVISC were studied in patients ≥40 years old in the three concurrently controlled clinical trials. The three studies investigated a total of 136 patients and 81 men. The demographics of trial participants were comparable across treatment groups with regard to age, gender and duration of osteoarthritis, except that there was a significantly greater (p = 0.04) number of men in the SYNVISC group and women in the control group in one study (see Table 1).

One study was a multicenter study conducted at four sites in Germany. This was a randomized, double-blind prospective clinical trial with two treatment groups. The study compared the safety and effectiveness of three weekly intra-articular injections of SYNVISC and of physiological saline in 103 subjects (109 knees) with osteoarthritis of the knee over a 26-week period.

A significantly greater number of saline-treated patients took concurrent osteoarthritis medications than did patients treated with SYNVISC (see Table 2). While both the SYNVISC and the saline-treated groups improved significantly as compared to baseline in all effectiveness measures, the SYNVISC treatment group showed a significantly greater improvement in all outcome measures than did the saline-treated patients over a 26-week period (see Tables 3A and 3B).

A second study was conducted at a single center in Germany as a concurrently controlled, randomized, double-blind prospective clinical trial with two treatment groups. This study compared the safety and effectiveness over a 26-week period of three weekly intra-articular injections of SYNVISC and of physiological saline in 29 subjects (29 knees) with osteoarthritis of the knee. The results of the study were similar to those in the German multicenter study, except that the salicylates, levels in most comparisons were smaller (see Tables 3A and 3B). In both of these studies the most pain relief and the greatest amount of treatment success occurred 8 to 12 weeks after SYNVISC treatment began.

Investigators obtained data at 26 weeks by telephone interviews. A validation study suggested that the results obtained in telephone interviews are equivalent to those obtained in office visits. Since investigators did not follow patients beyond week 26, the duration of pain relief beyond 26 weeks is not known.

A third study was a prospective, concurrently controlled, randomized, double-blind multicenter study conducted in 90 subjects (103 knees) at five U.S. sites. The study compared the safety and
effectiveness of three weekly intra-articular injections of SYNVISC and of three weekly arthrocenteses in subjects with osteoarthritis of the knee over a four-week period after the first injection or arthrocentesis. Both the SYNVISC-treated and the arthrocentesis-treated groups improved significantly as compared to baseline in all effectiveness measures. However, there were no significant differences between the SYNVISC-treated and arthrocentesis-treated patients at any time during the four-week evaluation period (see Tables 3A and 3B).

Covariate analyses with the covariates of center, presence or absence of previous treatments, baseline levels of outcome measures, age, gender, body mass, effusion, baseline X-ray score, duration of osteoarthritis, treatment of contralateral knee, and presence or absence of concurrent therapies, did not reveal any factors that significantly affected the results of any of the three studies. The German studies and the U.S. study differed in several respects, including inclusion of patients with effusions, length of no treatment period prior to SYNVISC injection, nature of control treatment, final evaluation time, mean duration of disease, mean weight, prior treatments for OA, pain and X-ray inclusion criteria. Thus, the German and the U.S. studies, which gave different results, investigated different patient populations and compared SYNVISC with different control treatments. Although success criteria for safety were not specified in any of the three studies, adverse events were encountered in each study. These events are included in the "Adverse Events" section.

**DETAILED DEVICE DESCRIPTION**

SYNVISC contains hylan A (average molecular weight 6,000,000) and hylan B hyaluronate in a buffered physiological sodium chloride solution, pH 7.2. SYNVISC has an elasticity (storage modulus G’) at 2.5 Hz of 111 ± 13 Pascal (Pa) and a viscosity (loss modulus G”) of 23 ± 2 Pa (elasticity and viscosity of knee synovial fluid of 18 to 27-year-old humans measured with a comparable method at 2.5 Hz; G’ = 117 ± 13 Pa; G” = 45 ± 8 Pa.)

Each 2.25 mL syringe of SYNVISC contains:
- Hylan polymers (hylan A + hylan B) 16 mg
- Sodium chloride 17 mg
- Disodium hydrogen phosphate 0.32 mg
- Sodium dihydrogen phosphate monohydrate 0.08 mg
- Water for injection q.s. to 2.0 mL

**HOW SUPPLIED**

SYNVISC is supplied in a 2.25 mL glass syringe containing one 2 mL (16 mg) dose of hylan G-F 20.

The contents of the syringe are sterile and nonpyrogenic.

**DIRECTIONS FOR USE**

SYNVISC is administered by intra-articular injection once a week (one week apart) for a total of three injections. 

**Precaution:** Do not use SYNVISC if the package has been opened or damaged. Store in original packaging (protected from light) at room temperature below 86° F (30°C). DO NOT FREEZE.

**Precaution:** The syringe containing SYNVISC is intended for single use. The contents of the syringe must be used immediately after the syringe has been removed from its packaging.

**Precaution:** Do not concomitantly use disinfectants containing quaternary ammonium salts for skin preparation because hyaluronan can precipitate in their presence.

**Precaution:** SYNVISC is administered by intra-articular injection once a week (one week apart) for a total of three injections. Strict aseptic administration technique must be followed.

- Using an 18- to 22-gauge needle, remove synovial fluid or effusion before each SYNVISC injection.
- Do not use the same syringe for removing synovial fluid and for injecting SYNVISC however the same 18- to 22-gauge needle should be used.
- Twist the tip cap before pulling it off, as this will minimize product leakage.
- To ensure a tight seal and prevent leakage during administration, secure the needle tightly while firmly holding the luer hub.

**Precaution:** Do not use or inject excessive leverage when attaching the needle or removing the needle guard as this may break the syringe tip.

- Inject the full 2 mL in one knee only.

**MANUFACTURED AND DISTRIBUTED BY:**

Genzyme Corporation
1125 Pleasant View Terrace
Ridgefield, New Jersey 07657
Telephone: 1-888-3-SYNVISC (1-888-379-6847)
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**PATIENT INFORMATION**

**SYNVISC**

**HYLAN G-F 20**

Be sure to read the following important information carefully. This information does not take the place of your doctor’s advice. If you do not understand this information or want to know more, ask your doctor.

**Glossary of Terms**

**Hyaluronan (pronounced hy-ul-OROE-nan):** is a natural substance that is present in very high amounts in joints. It acts like a lubricant and a shock absorber in the joint and is needed for the joint to work properly.

**Osteoarthritis (pronounced OS-te-o-ar-thi-RIS-tis):** is a type of arthritis that involves the wearing down of cartilage (the protective covering on the ends of your bones) and loss of cushioning fluid in the joint.

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- Drug therapy
- What adverse events were observed in the clinical studies?
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**What is the SYNVISC® product?**

SYNVISC is a gel-like mixture that is made up of hylan A fluid, hylan B gel, and salt water. Hylan A and hylan B are made from a substance called hyaluronan (hyaluronic acid—ROE-nan), also known as sodium hyaluronate that comes from chicken combs. Hyaluronan is a natural substance found in the body and is present in very high amounts in joints. The body’s own hyaluronan acts like a lubricant and a shock absorber in the joint and is needed for the joint to work properly.

**Osteoarthritis (pronounced os-TE-o-ar-THRI-tis) (OA) is a type of arthritis that involves the wearing down of cartilage (the protective covering on the ends of your bones). In OA, there may not be enough hyaluronan, and there may be a decrease in the quality of the hyaluronan in the joint. SYNVISC comes in syringes containing 2 mL (half a teaspoon) of product. SYNVISC is injected directly into your knee.

**How is the SYNVISC® product used? (Indications)**

The FDA-approved indication for SYNVISC is:

SYNVISC 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.

**How is the SYNVISC® product given?**

Your doctor will inject SYNVISC into your knee.

**Are there any reasons why I should not receive SYNVISC® injections? (Contraindications)**

Your doctor will determine if there is any reason why you are not an appropriate candidate for SYNVISC. You should be aware that:

- Should not be used in patients who have had any prior allergic reactions to SYNVISC, Synvisc-One® or any hyaluronan-based products. Signs of an allergic reaction may include swelling of your face, tongue, or throat; difficulty breathing or swallowing; shortness of breath; wheezing; chest pain; a tightness in your throat; sleepiness; rash; itching; hives; flushing; and/or fever.
- Should not be used in patients with a knee joint infection, skin disease or infection around the area where the injection will be given.

**What should my doctor warn me about?**

The following are important treatment considerations for you to discuss with your doctor and understand in order to help avoid unsatisfactory results and complications:

- SYNVISC is only for injection into the knee, performed by a doctor or other qualified health care professional. SYNVISC has not been tested to show pain relief in joints other than the knee.
- SYNVISC has not been tested to show better pain relief when combined with other injected medicines.
- Tell your doctor if you are allergic to products from birds such as feathers, eggs, and poultry.
- Tell your doctor if you have significant swelling or blood clots in the leg.
- SYNVISC should be used with caution when there is evidence of lymphatic or venous stasis in the leg to be injected.
- SYNVISC has not been tested in pregnant women, or women who are nursing. You should tell your doctor if you think you are pregnant, or if you are nursing a child.
- SYNVISC has not been tested in children (≤ 21 years of age).

**What are the risks of getting SYNVISC® injections?**

The side effects (also called reactions) sometimes seen when SYNVISC is injected into the knee as a first or repeat set of injections were pain, swelling, heat, redness, and/or fluid build-up around the knee. These reactions are generally mild and did not last long. If you have a reaction where the swelling is extensive and painful you should notify your doctor. The reactions seemed to occur more often when SYNVISC was injected into the knee as a repeat set of injections than when SYNVISC was injected as a first set of injections. Reactions are generally treated by resting and applying ice to the injected knee. Sometimes it is necessary to give pain relievers by mouth such as aspirin, ibuprofen or NSAID, or to give injections of steroids, or to remove fluid from the knee joint. Patients who have had arthroscopy (a surgical inspection of the knee joint) or other medical procedures related to these reactions.

Other less common side effects have been: rash, hives, itching, muscle pain/cramps, flushing and/or swelling of your face, fast heart beat, nausea (or feeling sick to your stomach), dizziness, fever, chills, headache, difficulty breathing, swelling in your arms and/or legs, prickly feelings in your skin, and/or a rare condition called anaphylaxis (a reaction where the swelling is extensive and painful), is a type of allergic reaction where the swelling is extensive and painful. If you have a reaction where the swelling is extensive and painful you should notify your doctor. The reactions seemed to occur more often when SYNVISC was injected into the knee as a repeat set of injections than when SYNVISC was injected as a first set of injections. Reactions are generally treated by resting and applying ice to the injected knee. Sometimes it is necessary to give pain relievers by mouth such as aspirin, ibuprofen or NSAID, or to give injections of steroids, or to remove fluid from the knee joint. Patients who have had arthroscopy (a surgical inspection of the knee joint) or other medical procedures related to these reactions.

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happened to you after receiving an injection of SYNVISC or other hyaluronan products. If any of the above symptoms or signs appear after you are given SYNVISC, or if you have any other problems, you should call your doctor. Rare cases of joint infection have been reported after SYNVISC injections.

What are the benefits of getting SYNVISC® injections?
As shown in medical studies of patients with osteoarthritis (OA) of the knee, where approximately half received a single injection of SYNVISC and the other half either had fluid removed from the knee and/or received injections of the same volume of saline water (“Saline Control” injection), the major benefits of SYNVISC are pain relief and improvement in other symptoms related to OA of the knee.

What is the principal benefit of SYNVISC injections?
The principal benefit of SYNVISC injections was pain relief which continued for three weeks after SYNVISC treatment started.

What other treatments are available for OA?
If you have OA, there are other things you can do besides getting SYNVISC. These include:

Non-drug treatments
- Avoiding activities that cause knee pain
- Exercise or physical therapy
- Weight loss
- Removal of excess fluid from your knee

Drug therapy
- Pain relievers such as acetaminophen and narcotics
- Drugs that reduce inflammation (signs of inflammation are swelling, pain or redness), such as aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs, for example ibuprofen and naproxen)
- Steroids that are injected directly into your knee.

What did the clinical studies show?
Two medical studies involving a total of 132 patients were done in Germany. The patients in these studies were at least 40 years old and received the complete treatment course. The patients were placed into one of two groups. One group was given an injection of SYNVISC into one or both knees once a week for three weeks. The second group had knee pain due to OA. The patients in these studies were at least 40 years old and received the complete treatment course.

What adverse events were observed in the clinical studies?
The side effects (also called reactions) sometimes seen when SYNVISC is injected into the knee as a first or repeat set of injections were pain, swelling, heat, redness, and/or fluid build-up around the knee. These reactions were generally mild and did not last long. Allergic reactions some which can be potentially severe, were observed during the use of Synvisc.

How do I get more information about the SYNVISC® product? (User Assistance)
If you have any questions or would like to find out more about SYNVISC, you may call Genzyme Corporation at 1-888-3-SYNVISC (1-888-379-6847) or visit www.synvisc.com.

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Genzyme Corporation
1125 Pleasant View Terrace
Ridgefield, New Jersey 07657
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Revised May 2023

<table>
<thead>
<tr>
<th>TABLE 1 DEMOGRAPHIC DATA*</th>
<th>DEMOGRAPHIC VARIABLE</th>
<th>Age</th>
<th>Gender [N* (%)]</th>
<th>Duration of Osteoarthritis (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=109</td>
<td>M (25%)</td>
<td>27</td>
<td>5 (10%)</td>
<td>22 (39%)</td>
</tr>
<tr>
<td>N=52</td>
<td>4 (9%)</td>
<td>13</td>
<td>6 (11%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>N=57</td>
<td>3 (5%)</td>
<td>6</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>P (Synvisc/Control)</td>
<td>0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>U.S. Multicenter†</td>
<td>Synvisc</td>
<td>62.9</td>
<td>17</td>
<td>27</td>
</tr>
<tr>
<td>Arthrocenteses</td>
<td>67.1</td>
<td>12</td>
<td>30</td>
<td>7.9</td>
</tr>
<tr>
<td>P (Synvisc/Athrocenteses)</td>
<td>0.06</td>
<td>0.3</td>
<td>0.5</td>
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</table>

* Patients ≥40 years old and received the complete treatment course
† Individual patients may be represented by more than one therapy
‡ Number and percentage of subjects
§ Medications not approved in the U.S.
¶ N = number of knees
# No concurrent therapies were recorded
° Data not collected
† Only acetaminophen was allowed

<table>
<thead>
<tr>
<th>TABLE 2 CONCURRENT OSTHEOARTHRITIS THERAPIES*</th>
<th>CONCURRENT MEDICATIONS*</th>
<th>TREATED KNEES</th>
<th>TOTAL</th>
<th>Synvisc</th>
<th>Control</th>
<th>P Synvisc/Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>German Multicenter</td>
<td>N=109</td>
<td>N=52</td>
<td>N=57</td>
<td>0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medications [N (97%)]</td>
<td>27 (25%)</td>
<td>5 (10%)</td>
<td>22 (39%)</td>
<td>0.03</td>
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<td></td>
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<tr>
<td>NSAIDS</td>
<td>17 (16%)</td>
<td>4 (9%)</td>
<td>13 (23%)</td>
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<tr>
<td>Acetaminophen</td>
<td>7 (6%)</td>
<td>4 (9%)</td>
<td>6 (11%)</td>
<td>0.09</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other medications§</td>
<td>3 (3%)</td>
<td>3 (5%)</td>
<td>0 (0%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>German Single Center</td>
<td>N=29</td>
<td>N=14</td>
<td>N=15</td>
<td>NA</td>
<td></td>
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<td>Any concurrent medication [ N (%)]</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td>U.S. Multicenter</td>
<td>N=103</td>
<td>N=51</td>
<td>N=52</td>
<td>0.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acetaminophen</td>
<td>100 (97 %)</td>
<td>50 (98%)</td>
<td>50 (96%)</td>
<td></td>
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</tr>
</tbody>
</table>

* Patients ≥40 years old and received the complete treatment course
† Individual patients may be represented by more than one therapy
‡ Number and percentage of subjects
§ Medications not approved in the U.S.
¶ N = number of knees
# No concurrent therapies were recorded
° Data not collected
† Only acetaminophen was allowed
### TABLE 3A EFFECTIVENESS OF WEIGHT-BEARING PAIN EVALUATED BY PATIENTS

<table>
<thead>
<tr>
<th>Week</th>
<th>Baseline</th>
<th>Improvement (Change from Baseline)</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>German Multicenter Synvisc-treated Mean</td>
<td>69.7</td>
<td>12.0</td>
</tr>
<tr>
<td>p‡</td>
<td>0.0001</td>
<td>0.0001</td>
</tr>
<tr>
<td>Saline-treated Mean</td>
<td>75.1</td>
<td>9.0</td>
</tr>
<tr>
<td>p‡</td>
<td>0.0001</td>
<td>0.0001</td>
</tr>
<tr>
<td>P*</td>
<td>0.1</td>
<td>0.3</td>
</tr>
<tr>
<td>German Single Center Synvisc-treated Mean</td>
<td>65.2</td>
<td>10.6</td>
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<tr>
<td>p‡</td>
<td>0.02</td>
<td>0.0001</td>
</tr>
<tr>
<td>Saline-treated Mean</td>
<td>69.8</td>
<td>5.4</td>
</tr>
<tr>
<td>p‡</td>
<td>0.01</td>
<td>0.0001</td>
</tr>
<tr>
<td>P*</td>
<td>0.4</td>
<td>0.2</td>
</tr>
<tr>
<td>U.S. Multicenter Synvisc-treated Mean</td>
<td>67.3</td>
<td>12.9</td>
</tr>
<tr>
<td>p‡</td>
<td>0.0002</td>
<td>0.0001</td>
</tr>
<tr>
<td>Arthrocenteses Mean</td>
<td>69.4</td>
<td>9.4</td>
</tr>
<tr>
<td>p‡</td>
<td>0.01</td>
<td>0.0001</td>
</tr>
<tr>
<td>P*</td>
<td>0.6</td>
<td>0.5</td>
</tr>
</tbody>
</table>

* Patients ≥40 years old and received the complete treatment course
† Week 26 data based on patient telephone interviews rather than patient office visit
‡ Mean of assessments on VAS of 0 to 100 mm
§ NA = no measurement taken
¶ Significance from baseline
# Significance between Synvisc and control

### TABLE 3B EFFECTIVENESS OF NIGHT PAIN EVALUATED BY PATIENTS

<table>
<thead>
<tr>
<th>Week</th>
<th>Baseline</th>
<th>Improvement (Change from Baseline)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
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</tr>
<tr>
<td>German Multicenter Synvisc-treated Mean</td>
<td>41.6</td>
<td>9.2</td>
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<tr>
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<td>0.0001</td>
</tr>
<tr>
<td>Saline-treated Mean</td>
<td>45.7</td>
<td>9.5</td>
</tr>
<tr>
<td>p‡</td>
<td>0.0001</td>
<td>0.0001</td>
</tr>
<tr>
<td>P*</td>
<td>0.5</td>
<td>0.9</td>
</tr>
<tr>
<td>German Single Center Synvisc-treated Mean</td>
<td>31.8</td>
<td>8.4</td>
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<tr>
<td>p‡</td>
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</tr>
<tr>
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<tr>
<td>P*</td>
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<td>0.4</td>
</tr>
<tr>
<td>U.S. Multicenter Synvisc-treated Mean</td>
<td>61.0</td>
<td>19.0</td>
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<tr>
<td>p‡</td>
<td>0.0001</td>
<td>0.0001</td>
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<tr>
<td>Arthrocenteses</td>
<td>Baseline</td>
<td>Improvement (Change from Baseline)</td>
</tr>
<tr>
<td>----------------</td>
<td>----------</td>
<td>----------------------------------</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mean</td>
</tr>
<tr>
<td></td>
<td></td>
<td>P</td>
</tr>
<tr>
<td>Mean</td>
<td>76.0</td>
<td>0.002</td>
</tr>
</tbody>
</table>

* Patients ≥40 years old and received the complete treatment course
† Week 26 data based on patient telephone interviews rather than patient office visit
‡ Mean of assessments on VAS of 0 to 100 mm
§ NA = no measurement taken
¶ Significance from baseline
# Significance between Synvisc and control

HYL-FSPL-SL-MAY23