MEDICA DEPOT

SYNVISC®
Product Specifications

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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® (hylan G-F 20) is an elastoviscous high molecular weight fluid containing hylan A and hylan B polymers produced from chicken combs. Hylans are 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 if 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, paresthesia, 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

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 39 reports in 37 patients (2.2% of injections, 7.2% of patients) of knee pain and/or swelling after these injections. Ten patients (10 knees) were treated with arthrocentesis and removal of joint effusion. Two additional patients (two knees) received treatment with intra-articular steroids. Two patients (two knees) received NSAIDs. One of these patients also received arthrocentesis. One patient was treated with arthroscopy. The remaining patients with adverse events localized to the knee received no treatment or only analgesics.

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 that occurred after injections that patients had received 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 events localized to the injected knee that have occurred after 4.4% and 8.5% 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 effusion 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.

Rarely, 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 38 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 appeared during the post-marketing period. One of these trials included 48 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 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 edema, muscle pain, tonsillitis with nausea, tachyarrythmia, phlebitis with varicosities and low back sprain.

Postmarket Experience

Other adverse events reported include: rash, *hives*, itching, *fever*, nausea, *headache, dizziness, chills*, muscle cramps, *paresthesia*, 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 women 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 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 conducted at a single center in Germany was 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 significance 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 enumerated 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 hydrated gel in a buffered physiological sodium chloride solution, pH 7.2. SYNVISC has an elasticity (storage modulus G') at 2.5 Hz of 111 ± 13 Pascals (Pa) and a viscosity (loss modulus G″) of 25 ± 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.

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 over tighten or apply 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:

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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-al-u-ROE-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.

Non-steroidal anti-inflammatory drugs: also known as ″NSAIDs″; medication used to treat pain or swelling. There are many examples of NSAIDs, including (but not limited to) aspirin and ibuprofen. Some of these are over-the-counter drugs, and some can only be obtained by prescription.

Osteoarthritis (pronounced OS-te-o-arth-RI-tis): (OA) 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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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 (pronounced hy-al-u-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 SYNVISC:

- 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 were 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 acetaminophen or NSAIDs, or to give injections of steroids, or to remove fluid from the knee joint. Patients rarely undergo arthroscopy (a surgical inspection of the knee joint) or other medical procedures related to these reactions.

Other less common side effects have been: rashes, 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 feeling of your skin, and in rare cases a low number of platelets in the blood (platelets are a type of blood cell that are needed to help clot your blood when you are cut or injured). Allergic reactions, some which can be potentially severe, were observed during the use of Synvisc. Before you are given SYNVISC, tell your doctor if something like this has ever

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 knee 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 salt water (a ″Saline Control″ injection), the major benefits of SYNVISC are pain relief and improvement in other symptoms related to OA of the knee.

What do I need to do after I get a SYNVISC® injection?

It is recommended you avoid strenuous activities (for example, high-impact sports such as soccer, tennis or jogging) or prolonged weight-bearing activities for approximately 48 hours following the injection. You should consult your doctor regarding the appropriate time to resume such activities.

Tell your doctor straight away if you develop skin disorder (such as change of color or open sores) after treatment with Synvisc.

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 had knee pain due to OA. The patients were placed in 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 was given an injection of salt water once a week for three weeks. As part of the study, knee joint pain was measured for 26 weeks. Also, patients and doctors were asked to judge the success of the treatment for 26 weeks. Patients with OA knee pain, who did not get pain relief with other medicines, got pain relief with SYNVISC. The patients given SYNVISC had more pain relief than the patients given salt water. Some patients started to feel pain relief after the first week of SYNVISC treatment. The most pain relief and the greatest amount of treatment success was seen 8 to 12 weeks after SYNVISC treatment started.

A medical study done in the United States involved 90 patients. The patients were at least 40 years old and had knee pain due to OA. Patients were placed into one of two groups. One group was given SYNVISC once a week for three weeks. The second group had a needle inserted into the knee to have any fluid removed (this procedure is called arthrocentesis [pronounced AR-thro-sen-TEE-sis]) once a week for three weeks.

Patients improved after SYNVISC treatment, but not more than patients who had arthrocentesis. This study was different from the German studies because the last time the two groups were compared was only two weeks after the last SYNVISC injection. The study was also different in other ways, including length of time that patients had to stop taking medicines before they could start treatment. The length of time patients had to stop taking medicines was two weeks in the German studies and four weeks in the U.S. study.

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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TABLE 1 DEMOGRAPHIC DATA*

	DEMOGRAPHIC VARIABLE			
	Age	Gender [N† (%)]		Duration of Osteoarthritis (years)
		M	F	
German Multicenter‡				
Synvisc	62.3	21 (45%)	26 (55%)	5.4
Saline	64.7	13 (25%)	39 (75%)	5.6
P (Synvisc/ Saline)	0.3	0.04		0.9
German Single Center				
Synvisc	59.8	10 (71%)	4 (29%)	2.4
Saline	59.5	8 (53%)	7 (47%)	2.5
P (Synvisc/ Saline)	0.9	0.3		1.0
U.S. Multicenter§				
Synvisc	62.9	17 (39%)	27 (61%)	8.9
Arthrocenteses	67.1	12 (29%)	30 (71%)	7.9
P (Synvisc/ Arthrocenteses)	0.06	0.3		0.5

* Patients ≥40 years old and received the complete treatment course
† N = number of patients
‡ In addition, 1 male and 3 females were treated with Synvisc in one knee and saline in the other
§ In addition, 4 females were treated with Synvisc in one knee and arthrocenteses in the other

TABLE 2 CONCURRENT OSTHEOARTHRITIS THERAPIES*

CONCURRENT MEDICATIONS†	TREATED KNEES			
	TOTAL	Synvisc	Control	P Synvisc/ Control
German Multicenter Medications [N (%)]‡ NSAIDS Acetaminophen Other medications§	N¶=109 27 (25%) 17 (16%) 7(6%) 3 (3%)	N=52 5 (10%) 4 (8%) 1 (2%) 3 (5%)	N=57 22 (39%) 13 (23%) 6 (11%) 0 (0%)	0.001 0.03 0.07 0.09
German Single Center# Any concurrent medication [N (%)]	N=29 NAÞ	N=14 NA	N=15 NA	NA
U.S. Multicenterß Acetaminophen [N (%)]	N=103 100 (97 %)	N=51 50 (98%)	N=52 50 (96%)	0.6

* 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
Þ Data not collected
ß Only acetaminophen was allowed

TABLE 3A EFFECTIVENESS OF WEIGHT-BEARING PAIN* EVALUATED BY PATIENTS

	Baseline	Improvement (Change from Baseline)						
Week	0	1	2	3	4	8	12	26†
German Multicenter Synvisc-treated								
Mean‡	69.7	12.0	26.5	37.9	NA§	45.9	46.5	34.0
P¶		0.0001	0.0001	0.0001		0.0001	0.0001	0.0001
Saline-treated								
Mean	75.1	9.0	17.0	23.0	NA	16.8	16.4	19.1
P¶		0.0001	0.0001	0.0001		0.0001	0.0002	0.0001
P#	0.1	0.3	0.01	0.0008	NA	<0.0001	<0.0001	0.005
German Single Center Synvisc-treated								
Mean	65.2	10.6	31.8	43.9	NA	51;7	53.5	44.5
P¶		0.02	0.0001	0.0001		0.0001	0.0001	0.0001
Saline-treated								
Mean	69.8	5.4	19.3	25.4	NA	24;4	26.8	21.2
P¶		0.01	0.0001	0.0001		0.0001	0.0001	0.002
P#	0.4	0.2	0.03	0.01	NA	0.0001	0.0001	0.001
U.S. Multicenter Synvisc-treated								
Mean	67.3	12.9	18.9	NA	21.3	NA	NA	NA
P¶		0.0002	0.0001		0.0001			
Arthrocenteses								
Mean	69.4	9.4	21.2	NA	19.1	NA	NA	NA
P¶		0.01	0.0001		0.0002			
P#	0.6	0.5	0.7	NA	0.7	NA	NA	NA

* 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

	Baseline	Improvement (Change from Baseline)						
Week	0	1	2	3	4	8	12	26†
German Multicenter Synvisc-treated								
Mean‡	41.6	9.2	20.0	26.4	NA§	28.3	29.8	24.3
P¶		0.0001	0.0001	0.0001		0.0001	0.0001	0.0001
Saline-treated								
Mean	45.7	9.5	15.2	21.2	NA	18.4	17.3	12.8
P¶		0.0001	0.0001	0.0001		0.0001	0.0001	0.002
P#	0.5	0.9	0.2	0.3	NA	0.05	0.02	0.03
German Single Center Synvisc-treated								
Mean	31.8	8.4	17.7	24.8	NA	28.9	29.5	25.4
P¶		0.04	0.005	0.004		0.005	0.005	0.004
Saline-treated								
Mean	33.3	4.5	13.1	16.1	NA	16.1	17.9	14.9
P¶		0.1	0.001	0.0007		0.0001	0.0001	0.01
P#	0.9	0.4	0.4	0.3	NA	0.1	0.2	0.2
U.S. Multicenter Synvisc-treated								
Mean	61.0	19.0	17.9	NA	22.8	NA	NA	NA
P¶		0.0001	0.0001		0.0001			

TABLE 3B EFFECTIVENESS OF NIGHT PAIN* EVALUATED BY PATIENTS (continued)

	Baseline	Improvement (Change from Baseline)						
Arthrocenteses								
Mean	76.0	23.3	36.3	NA	29.8	NA	NA	NA
P¶		0.0001	0.0001		0.0001			
P#	0.002	0.5	0.004	NA	0.3	NA	NA	NA

* 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

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