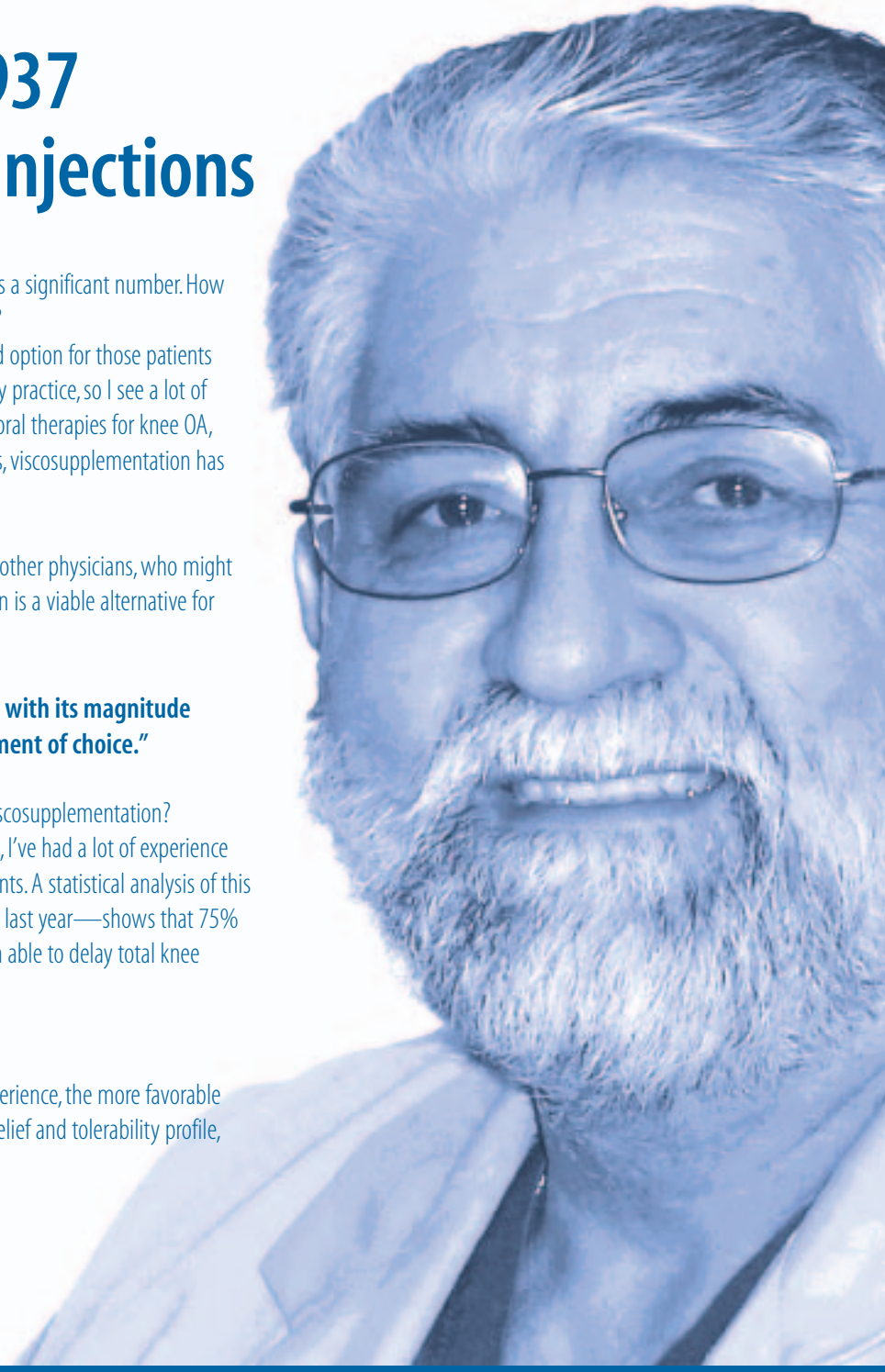
About Dr Waddell

A leading orthopedic surgeon, Dr Waddell is a member of one of the largest orthopedic clinics in the southern United States. His practice focuses on disorders of the knee, arthroscopy, joint replacement, sports medicine, and general orthopedics. He is one of the most experienced physicians in the country regarding the use of viscosupplementation in the treatment of osteoarthritis (OA) knee pain—with over 2,500 patients treated—and the author of numerous articles on the subject. A Fellow of the American Academy of Orthopaedic Surgeons (AAOS), Dr Waddell has been certified by the American Board of Orthopaedic Surgery since 1980.

The Leadership Forum would like to thank Dr Waddell for participating in this interview.

OSTEOARTHRITIS LEADERSHIP FORUM

Learnings From 12,937 SYNVISC® (hylan G-F 20) Injections



Leadership Forum (LF): Over 12,000 SYNVISC injections— that's a significant number. How has viscosupplementation changed the way you treat OA knee pain?

David Waddell (DW): It's given me an effective and well-tolerated option for those patients who have failed on other conservative treatments. I have a knee-only practice, so I see a lot of patients who have already run the range of nonpharmacologic and oral therapies for knee OA, including physical therapy, analgesics, and NSAIDs. For these patients, viscosupplementation has become one of my primary treatment considerations.

I also see a significant portion of patients, referred to my practice by other physicians, who might otherwise be candidates for knee replacement. Viscosupplementation is a viable alternative for those patients who would like to avoid, or at least delay, surgery.

"…the more favorable dosing schedule of SYNVISC, combined with its magnitude of pain relief and tolerability profile, makes it my viscosupplement of choice."

LF: So you've seen a delay in the need for knee replacement with viscosupplementation?

DW: Yes. Being one of the earliest adopters of viscosupplementation, I've had a lot of experience with this treatment and have built up a significant database of patients. A statistical analysis of this data—which was presented in a poster at the AAOS in Washington last year—shows that 75% of patients receiving viscosupplementation in my practice have been able to delay total knee replacement by 3.8 years.[1] The impact on patients is considerable.

LF: Do you have a preference among viscosupplement products?

DW: I've used 3 of the viscosupplements at various times. In my experience, the more favorable dosing schedule of SYNVISC, combined with its magnitude of pain relief and tolerability profile, makes it my viscosupplement of choice.

OA PERSPECTIVES

Q&A WITH DAVID D. WADDELL, MD

As a matter of fact, I've had 3 courses of treatment with SYNVISC myself. The first course got me completely off COX-2s and left me largely symptom free. And the repeat courses—administered in both of my knees—were well tolerated.

Dr Waddell is also a SYNVISC patient, having received 3 courses over the past 5 years.

LF: What advice would you give to your peers when treating their patients with viscosupplements?

DW: I believe that follow-up can mean the difference between short-term relief and longer-term OA management. Some doctors will give an injection and tell the patient, "Come back to see me if you need to." With a majority of our patients, we see them again 30 days, 3 months, 6 months after treatment—and then on an annual basis. In that way, we can assess their response, monitor their condition, and modify the treatment as needed—whether it means physical therapy, change of activities, or additional treatments.

I might also suggest they consider SYNVISC. Most important, no other viscosupplement has given my patients a greater magnitude of pain relief. In addition, the simpler dosing regimen of SYNVISC is an advantage to both my patients and myself.

Please see accompanying full Prescribing Information.

SYNVISC® (hylan G-F 20) 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, eg, acetaminophen. In clinical trials, the most commonly reported adverse events were transient local pain, swelling, and/or effusion in the injected knee. In some cases, these symptoms have been extensive. Other side effects such as rash have been reported rarely.

SYNVISC is contraindicated in patients with known hypersensitivity to hyaluronan products or patients with infections in or around the knee. Use caution when using SYNVISC in patients allergic to avian proteins, feathers, or egg products; who have evidence of venous or lymphatic stasis in the leg to be treated; or who have severe inflammation in the knee joint to be treated. Patients should be advised to avoid strenuous or prolonged weight-bearing activities after treatment. Strict adherence to aseptic technique must be followed to avoid joint infection. The safety and effectiveness of SYNVISC in children and in pregnant or lactating women have not been established. It is unknown whether SYNVISC is excreted in human milk.

Reference: 1. Waddell DD, Bricker DC, on behalf of Orthopedic Specialists of Louisiana, Shreveport, LA. Total knee replacement delayed during six years of hylan G-F 20 use in orthopedic practice [poster]. Presented at: American Academy of Orthopaedic Surgeons Annual Meeting. Washington, DC, February 2005.

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genzyme Biosurgery
A division of Genzyme Corporation
55 Cambridge Parkway
Cambridge, MA 02142
1-888-3SYNVISC
www.synvisc.com

SYNVISC HYLAN G-F 20

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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.

WHAT IS SYNVISC?

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 hye-a-loo-ROE-nan), also known as sodium hyaluronate that comes from chicken combs. This 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.

70230604 Revised December 15, 2006

WHAT IS SYNVISC USED FOR?

Synvisc is used to relieve knee pain due to OA. It is used for patients who do not get enough relief from simple painkillers, such as acetaminophen, or from exercise and physical therapy.

WHAT ARE THE BENEFITS OF SYNVISC?

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-TE-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 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
- physical therapy
- 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) such as ibuprofen and naproxen
- steroids that are injected directly into your knee

ARE THERE ANY REASONS WHY YOU SHOULD NOT RECEIVE SYNVISC?

- You should not get this product if you have had any allergic

reaction before to Synvisc or hyaluronan 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. You should call your doctor immediately if you develop any of these signs of an allergic reaction.

- You should not be given Synvisc if you have a knee joint infection or skin diseases or infections around the area where the injection will be given. Talk to your doctor if you have any questions about this information.

THINGS YOU SHOULD KNOW ABOUT SYNVISC:

- Synvisc is only for injection into the knee, performed by a doctor or other qualified health care professional.
- Tell your doctor if you are allergic to products from birds such as feathers, eggs, and poultry.
- After you receive the injection, you may need to avoid activities such as jogging, tennis, heavy lifting, or standing for a long time.
- 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.
- The safety and effectiveness of Synvisc have not been tested in children.

POSSIBLE SIDE EFFECTS:

- 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, but sometimes fluid accumulation was considerable and painful; cases where the swelling is extensive and painful should be discussed with 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.
- These reactions were generally treated by giving pain relievers by mouth such as acetaminophen or by giving NSAIDs by mouth or injections of steroids, or by removing fluid from the knee joint. Patients have rarely undergone arthroscopy (a surgical inspection of the knee joint) and other medical procedures.
- Rare cases of knee joint infection have been reported after Synvisc injections.
- Rashes, hives and itching have been seen in patients after Synvisc treatment. 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.
- Other less common side effects have been: muscle pain/cramps, flushing and/or swelling of your face, fast heartbeat, 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).
- 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.

HOW IS SYNVISC GIVEN?

Your doctor will give you your injection of Synvisc (2mL) into your knee once a week, for a total of three injections.

MANUFACTURED AND DISTRIBUTED BY:

Genzyme Biosurgery
a division of Genzyme Corporation
1125 Pleasant View Terrace
Ridgefield, New Jersey 07657

HOW DO I GET MORE INFORMATION ABOUT SYNVISC?

If you have any questions or would like to find out more about Synvisc, you may call Genzyme Biosurgery at 1-888-3-SYNVISC (1-888-379-6847).

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SYNVISC®
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 fluid containing hylan polymers produced from chicken combs. Hylans are derivatives of hyaluronan (sodium hyaluronate), a natural complex sugar of the glycosaminoglycan family. 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.

PRECAUTIONS

General

- The effectiveness of a single treatment cycle of less than three injections 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.
- Do not inject anesthetics or other medications into the knee joint during Synvisc therapy. Such medications may dilute Synvisc and affect its safety and effectiveness.
- 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.

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- 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 that leg.

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 or prolonged weight-bearing activities such as jogging or tennis following the intra-articular injection.

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.
- The safety and effectiveness of Synvisc have not been established in children.

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.

Postmarket Experience: The most common adverse events reported have been pain, swelling and/or effusion in the injected knee. In some cases the effusion was considerable and caused pronounced pain. In some instances, patients have presented with knees that were tender, warm and red. It is important to rule out infection or crystalline arthropathies in such cases. Synovial fluid aspirates of varying volumes have revealed a range of cell counts, from very few to over 50,000 cells/mm^3. Reported treatments included symptomatic therapy (e.g., rest, ice, heat, elevation, simple analgesics and NSAIDs) and/or arthrocentesis. Intra-articular corticosteroids have been used when infection was excluded. 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[1]; the other contained 71 patients who received 211 injections during a second course of Synvisc treatment.

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.[2,3]

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[4] 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 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 2 mL Synvisc.

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: Twist the tip cap before pulling it off, as this will minimize product leakage.

Precaution: Strict aseptic administration technique must be followed.

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

Precaution: Remove synovial fluid or effusion before each Synvisc injection.

Do not use the same syringe for removing synovial fluid and for injecting Synvisc, but the same needle should be used.

Take particular care to remove the tip cap of the syringe and needle aseptically.

Inject Synvisc into the knee joint through an 18 to 22 gauge needle.

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 tip of the syringe.

Do not inject anesthetics or any other medications intra-articularly into the knee while administering Synvisc therapy. This may dilute Synvisc and affect its safety and effectiveness.

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. Inject the full 2 mL in one knee only. If treatment is bilateral, a separate syringe must be used for each knee. Discard any unused Synvisc.

MANUFACTURED AND DISTRIBUTED BY:
Genzyme Biosurgery
a division of Genzyme Corporation
1125 Pleasant View Terrace
Ridgefield, New Jersey 07657
Telephone: 1-888-3-SYNVISC (1-888-379-6847)

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REFERENCE

[1] Raynauld JP, Bellamy N, Goldsmith CH, Tugwell P, Torrance GW, Pericak D. *et al.* An evaluation of the safety and effectiveness of repeat courses of hylan G-F 20 for treating patients with knee osteoarthritis. Osteoarthritis Research Society International, 2002 OARSI World Congress on Osteoarthritis, Sydney, Australia [Paper reference # PS128]. Presentation on File.

[2] Leopold SS, Warme WJ, Pettis PD and Shott S. Increased frequency of acute local reaction to intra- articular Hylan GF-20 (Synvisc) in patients receiving more than one course of treatment. J. Bone Joint Surg. 84-A (9): 1619-1623, 2002.

[3] Waddell DD, Estey DJ and Bricker D. Retrospective tolerance of Hylan G-F 20 using fluoroscopically-confirmed injection and effectiveness of retreatment in knee osteoarthritis. Proceedings of the American College of Rheumatology Annual Meeting 2001. Presentation on File.

[4] Scale, D., Wobig, M. and Wolpert, W. (1994). Viscosupplementation of osteoarthritic knees with hylan: a treatment schedule study. Curr Ther Res; 55:220-232.

TABLE 1 DEMOGRAPHIC DATA[1]

	DEMOGRAPHIC VARIABLE			
	Age	Gender [N[2] (%)]		Duration of Osteoarthritis (years)
		M	F	
German Multicenter[3]				
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[4]				
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

Footnotes: [1] Patients ≥ 40 years old and received the complete treatment course
[2] N = number of patients
[3] In addition, 1 male and 3 females were treated with Synvisc in one knee and saline in the other
[4] In addition, 4 females were treated with Synvisc in one knee and arthrocenteses in the other

TABLE 3A EFFECTIVENESS OF WEIGHT-BEARING PAIN[1] EVALUATED BY PATIENTS

	Base-line	Improvement (Change from Baseline)						
Week	0	1	2	3	4	8	12	26[6]
German Multicenter								
Synvisc-treated								
Mean[2]	69.7	12.0	26.5	37.9	NA[5]	45.9	46.5	34.0
P[3]		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[3]		0.0001	0.0001	0.0001		0.0001	0.0002	0.0001
P[4]	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[3]		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[3]		0.01	0.0001	0.0001		0.0001	0.0001	0.002
P[4]	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[3]		0.0002	0.0001		0.0001			
Arthrocenteses								
Mean	69.4	9.4	21.2	NA	19.1	NA	NA	NA
P[3]		0.01	0.0001		0.0002			
P[4]	0.6	0.5	0.7	NA	0.7	NA	NA	NA

Footnotes: [1] Patients ≥ 40 years old and received the complete treatment course
[2] Mean of assessments on VAS of 0 to 100 mm
[3] Significance from baseline
[4] Significance between Synvisc and control
[5] NA = no measurement taken
[6] Week 26 data based on patient telephone interviews rather than patient office visit

TABLE 2 CONCURRENT OSTEOARTHRITIS THERAPIES[1]

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

Footnotes: [1] Patients ≥ 40 years old and received the complete treatment course
[2] Individual patients may be represented by more than one therapy
[3] N = number of knees
[4] Number and percentage of subjects
[5] Medications not approved in the U.S.
[6] No concurrent therapies were recorded
[7] Data not collected
[8] Only acetaminophen was allowed

TABLE 3B EFFECTIVENESS OF NIGHT PAIN[1] EVALUATED BY PATIENTS

	Base-line	Improvement (Change from Baseline)						
Week	0	1	2	3	4	8	12	26[6]
German Multicenter								
Synvisc-treated								
Mean[2]	41.6	9.2	20.0	26.4	NA[5]	28.3	29.8	24.3
P[3]		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[3]		0.0001	0.0001	0.0001		0.0001	0.0001	0.002
P[4]	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[3]		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[3]		0.1	0.001	0.0007		0.0001	0.0001	0.01
P[4]	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[3]		0.0001	0.0001		0.0001			
Arthrocenteses								
Mean	76.0	23.3	36.3	NA	29.8	NA	NA	NA
P[3]		0.0001	0.0001		0.0001			
P[4]	0.002	0.5	0.004	NA	0.3	NA	NA	NA

Footnotes: [1] Patients ≥ 40 years old and received the complete treatment course
[2] Mean of assessments on VAS of 0 to 100 mm
[3] Significance from baseline
[4] Significance between Synvisc and control
[5] NA = no measurement taken
[6] Week 26 data based on patient telephone interviews rather than patient office visit

Revised December 15, 2006