Synvisc® Hylan G-F 20

CI 5014-1
8005US-01

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. One such systemic adverse event occurred following extra-articular injections of Synvisc in clinical use outside the U.S.
- 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.
- Remove synovial fluid or effusion, if present, before injecting Synvisc.
- 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 and/or swelling of the injected joint may occur after intra-articular injection of Synvisc.
- 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.
- The safety and effectiveness of repeat treatment cycles of Synvisc have not been established.

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

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.

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, tachyarrhythmia, phlebitis with varicosities and low back sprain.

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.

In clinical use in Canada (since 1992) and Sweden (since 1995), the most common adverse events reported have been pain, swelling, and/or effusion in the injected knees. Other adverse events reported were one case each of: generalized urticaria; recurring small hives; pain on one side of the body with nausea, anxiety and listlessness; facial flush with swelling of lips; nausea with dizziness; and shivering with headache, nausea, respiratory difficulties; and prickling in body which did not recur after subsequent Synvisc injections. No cases of anaphylaxis or anaphylactoid reactions have been reported. No deaths have been associated with the use of Synvisc. Intra-articular infections did not occur in any of the clinical trials, but have occurred in clinical use following Synvisc injections.

CLINICAL STUDIES

The safety and effectiveness of Synvisc was studied in patients ≥40 years old in the three concurrently controlled clinical trials referred to in the "Adverse Events" section. 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 were 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. It 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.

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 twelve-week period (See Table 3).

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 12-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).

A third study was a prospective, concurrently controlled, randomized, double-blinded 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- and the saline-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, and pain and X-ray inclusion criteria. Thus, 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 18-27 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.

Product Number: 0008-9149-02	3 disposable syringes

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: 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, if present, before injecting Synvisc.

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.

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.

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REFERENCE

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

TABLE 1
DEMOGRAPHIC DATA[1]

	DEMOGRAPHIC VARIABLE			
	Age	Gender [N[2] (%)]		Duration of Osteoarthritis (years)
		M	F	
German Multicenter[3]				
Synvisc[4]	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
Arthrocentesis	67.1	12 (29%)	30 (71%)	7.9
P (Synvisc/Arthrocentesis)	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 arthrocentesis in the other

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

	Base-line	Improvement (Change from Baseline)					
Week	0	1	2	3	4	8	12
German Multicenter							
Synvisc-treated							
Mean[2]	69.7	12.0	26.5	37.9	NA[5]	45.9	46.5
P[3]		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
P[3]		0.0001	0.0001	0.0001		0.0001	0.0002
P[4]	0.1	0.3	0.01	0.0008	NA	<0.0001	<0.0001
German Single Center							
Synvisc-treated							
Mean	65.2	10.6	31.8	43.9	NA	51.7	53.5
P[3]		0.02	0.0001	0.0001		0.0001	0.0001
Saline-treated							
Mean	69.8	5.4	19.3	25.4	NA	24.4	26.8
P[3]		0.01	0.0001	0.0001		0.0001	0.0001
P[4]	0.4	0.2	0.03	0.01	NA	0.0001	0.0001
U.S. Multicenter							
Synvisc-treated							
Mean	67.3	12.9	18.9	NA	21.3	NA	NA
P[3]		0.0002	0.0001		0.0001		
Saline-treated							
Mean	69.4	9.4	21.2	NA	19.1	NA	NA
P[3]		0.01	0.0001		0.0002		
P[4]	0.6	0.5	0.7	NA	0.7	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

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

	Base-line	Improvement (Change from Baseline)					
Week	0	1	2	3	4	8	12
German Multicenter							
Synvisc-treated							
Mean[2]	41.6	9.2	20.0	26.4	NA[5]	28.3	29.8
P[3]		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
P[3]		0.0001	0.0001	0.0001		0.0001	0.0001
P[4]	0.5	0.9	0.2	0.3	NA	0.05	0.02
German Single Center							
Synvisc-treated							
Mean	31.8	8.4	17.7	24.8	NA	28.9	29.5
P[3]		0.04	0.005	0.004		0.005	0.005
Saline-treated							
Mean	33.3	4.5	13.1	16.1	NA	16.1	17.9
P[3]		0.1	0.001	0.0007		0.0001	0.0001
P[4]	0.9	0.4	0.4	0.3	NA	0.1	0.2
U.S. Multicenter							
Synvisc-treated							
Mean	61.0	19.0	17.9	NA	22.8	NA	NA
P[3]		0.0001	0.0001		0.0001		
Saline-treated							
Mean	76.0	23.3	36.3	NA	29.8	NA	NA
P[3]		0.0001	0.0001		0.0001		
P[4]	0.002	0.5	0.004	NA	0.3	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

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