Table of Contents

1. SUMMARY OF SAFTETY AND EFFECTIVENESS

1.1 GENERAL INFORMATION

Device Generic Name:	Hylan G-F 20
Device Trade Name:	Synvisc-One™
Applicants Name:	Genzyme Corporation
Pre-market Approval (PMA) Application Number:	P940015
Date of Panel Recommendation:	To be completed by FDA
Date of Notice of Approval to the Applicant:	To be completed by FDA

The original PMA application P940015 for Synvisc® (hylan G-F 20) was approved on August 8, 1997. The device is indicated for the treatment of pain in OA of the knee in patients who have failed to respond adequately to conservative non-pharmacologic therapy and simple analgesics (e.g., acetaminophen). Preclinical data from the original application are applicable to the current PMA supplement for Synvisc-One™ (hylan G-F 20) and are therefore incorporated by reference. Please refer to the SSED for P940015 for additional supporting documentation. You may obtain a copy of the SSED via the CDRH website at http://www.fda.gov/cdrh/pdf/p940015b.pdf. Written requests for copies can be obtained from The Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20857 under Docket # 98M-0217.

1.2 INDICATIONS FOR USE

Synvisc-One is indicated for the treatment of pain in OA of the knee in patients who have failed to respond adequately to conservative non-pharmacologic therapy and simple analgesics e.g., acetaminophen.

1.3 CONTRAINDICATIONS

- Do not administer to patients with known hypersensitivity (allergy) to hyaluronan (sodium hyaluronate) preparations.

- Do not inject Synvisc-One in the knees of patients having knee joint infections or skin diseases or infections in the area of the injection site.

1.4 WARNINGS AND PRECAUTIONS

Precautions and warnings can be found in the device labeling.

1.5 DEVICE DESCRIPTION

Synvisc-One (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.

Synvisc-One contains three doses of hylan G-F 20 which contains hylan A (average molecular weight 6,000,000 Daltons) and hylan B hydrate (gel in a buffered physiological sodium chloride solution, pH 7.2. Synvisc-One 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 ± 8.2 Pa).

Synvisc-One is supplied in a 10-ml glass syringe containing 3 doses (6 ml) of hylan G-F 20. The contents of the syringe are sterile and non-pyrogenic.

Each syringe of Synvisc-One contains:

Hylan polymers (hylan A + hylan B)	48 mg
Sodium chloride	51 mg
Disodium hydrogen phosphate	0.96 mg
Sodium dihydrogen phosphate monohydrate	0.24 mg
Water for injection	q.s. to 6.0 ml

1.6 ALTERNATIVE PRACTICES AND PROCEDURES

For patients who have failed to respond adequately to conservative non-pharmacologic therapy and simple analgesics, e.g., acetaminophen, alternative therapies to Synvisc-One include: NSAIDs, IA injections of corticosteroids or injections of unmodified hyaluronan (sodium hyaluronate). For patients who have failed the above treatments, surgical interventions such as arthroscopic surgery and total knee replacement surgery are also alternative treatments.

1.7 MARKETING HISTORY

Synvisc which is the same material as Synvisc-One only in a 3-injection regimen has been commercially available for more than 10 years and is approved for sale in over 70 countries throughout the world.

Synvisc-One has not been marketed in any country to date.

Synvisc-One has not been withdrawn from marketing in any countries.

1.8 POTENTIAL ADVERSE EFFECTS

1.8.1 Adverse Events Involving the Injected Knee

Clinical Trial: A total of 253 (Synvisc-One: n=123, Placebo: n=130) patients were treated in the study. In the controlled clinical trial with Synvisc-One, the frequency and type of adverse events (AEs) were similar between the group of patients that received Synvisc-One and the group that received Placebo.

Initial Treatment Phase: The overall proportion of patients with AEs irrespective of treatment relatedness (Synvisc-One: n=70, 56.9%; Placebo: n=79, 60.8%) and with target knee AEs (Synvisc-One: n=44, 35.8%; Placebo: n=44, 33.8%) was comparable between the two treatment groups. There were 7 (5.7%) patients in the Synvisc-One group and 5 (3.8%) patients in the Placebo group who experienced AEs assessed as related to the study injection. There were 4 (3.3%) patients in the Synvisc-One group and 2 (1.5%) patients in the Placebo group who experienced AEs assessed as related to the study treatment.

Table 1-1: Patients with Adverse Events in the Injected Knee

MedDRA Preferred Term	Synvisc-One N=123 n (%)	Placebo N=130 n (%)	Total N=253 n (%)
Any Treatment-Emergent Adverse Event	44 (35.8%)	44 (33.8%)	88 (34.8%)
Arthralgia	31 (25.2%)	28 (21.5%)	59 (23.3%)
Joint stiffness	10 (8.1%)	13 (10.0%)	23 (9.1%)
Joint effusion	7 (5.7%)	7 (5.4%)	14 (5.5%)
Joint swelling	5 (4.1%)	7 (5.4%)	12 (4.7%)
Joint warmth	2 (1.6%)	5 (3.8%)	7 (2.8%)
Post-traumatic pain	0	3 (2.3%)	3 (1.2%)
Injection site pain	1 (0.8%)	1 (0.8%)	2 (0.8%)
Synovial cyst	0	2 (1.5%)	2 (0.8%)
Arthritis	1 (0.8%)	0	1 (0.4%)
Arthropathy	1 (0.8%)	0	1 (0.4%)
Gait disturbance	1 (0.8%)	0	1 (0.4%)
Joint range of motion decreased	0	1 (0.8%)	1 (0.4%)
Osteoarthritis	0	1 (0.8%)	1 (0.4%)

Note: Patients are counted once for each unique AE irrespective of treatment relatedness, and may have had more than one unique AE

Injected knee AEs assessed as related to study procedure occurred in 6 (4.9%) patients in the Synvisc-One group and in 4(3.1%) patients in the Placebo group. The number of patients with treatment-related AEs in the injected knee were 4 (3.3%) for the Synvisc-One group and 1 (0.8%) for the Placebo group.

Related AEs involving the injected knee were mild or moderate in nature. The most commonly reported AEs after IA injection of Synvisc-One or placebo were arthralgia, joint stiffness, joint effusion and joint swelling.

There were no serious AEs in the injected knee in either the Synvisc-One or the Placebo group.

Repeat Treatment Phase: The repeat treatment phase confirmed the safety profile of the Initial phase with no increase of AEs in patients receiving a second injection of Synvisc-One. One hundred and sixty patients were treated during this phase of the study, of which 77 patients received a second injection of Synvisc-One and 83 patients received an injection of Synvisc-One after receiving a placebo injection during the initial treatment

phase. The overall proportion of patients with Treatment Emergent AEs was Synvisc-One/ Synvisc-One: n=9, 11.7% and Placebo/ Synvisc-One: n=13, 15.7%.

In the Synvisc-One/ Synvisc-One group there was 1 (1.3%) patient who experienced target knee AEs assessed as related to the study treatment and 4 (5.2%) patients who experienced AEs related to the study injection. In the Placebo/ Synvisc-One group there were 6 (7.2%) patients who experienced target knee AEs related to the study treatment and 7 (8.4%) patients who experienced AEs related to the study injection.

Patients who developed target knee AEs during the initial phase of the study and who subsequently received repeat treatment did not experience target knee AEs on repeat exposure to Synvisc-One.

Overall Target Knee Safety Summary: The safety profile of Synvisc-One is similar to the Clinical and Post-marketing experience seen with Synvisc® where pain, swelling and effusion were the most frequently occurring AEs in the injected knee. There have been post market reports for Synvisc indicating that in some cases the joint effusion may be large and can cause pronounced pain; it is important to remove and to analyze the fluid to rule out infection or crystalline arthropathies. These types of severe AEs were not observed in either the initial or repeat treatment phase of the Synvisc-One trial. IA infections did not occur in any of the clinical trials of Synvisc/ Synvisc-One and have been reported only rarely during clinical use of Synvisc.

1.8.2 Adverse Events Outside of the Target Knee

Overall 101 patients (Synvisc-One: n=47, 38.2%; Placebo: n=54, 41.5%) experienced at least one AE outside the target knee irrespective of treatment relatedness. The most commonly occurring AEs outside the target knee were headache, back pain and nasopharyngitis. In the Synvisc-One group was one AE of syncope considered related to the study procedure and no AEs considered related to the study treatment.

Synvisc® 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.

No new systemic AEs were identified during this study as compared to the systemic AEs identified with Synvisc®.1

1.9 SUMMARY OF CLINICAL INVESTIGATIONS

1.9.1 Pilot Study

The treatment regimen for Synvisc-One was selected on the basis of a 100-patient pilot dose-ranging study in which three 2-ml doses (a total of 6 ml) of hylan G-F 20 delivered in one injection had preliminary efficacy trends similar to three 2-ml doses delivered in three injections over three weeks, and equal to or better than preliminary efficacy trends of several other dosing schedules tested.2

1.9.2 Pivotal Clinical Trial

Study Design: The safety and efficacy of Synvisc-One were investigated in a prospective, well-controlled randomized double-blind, 2-arm (parallel group) clinical trial3. A total of 253 patients were randomly assigned to study treatment at 21 sites in 6 countries; 123 received 6 ml of Synvisc-One and 130 received 6 ml of placebo (buffered saline solution). Neither the patients nor the clinical observers knew the patients' treatment allocations. The outcome measures collected included the WOMAC (LK 3.1 A) version)4, patient global assessment (PTGA), clinical observer global assessment (COGA), and use of rescue analgesic (see Treatment and Evaluation Schedule). The primary patient population analyzed for efficacy was intent-to-treat (ITT). The primary efficacy analysis was a comparison over 26 weeks between the two treatment groups of change from baseline in the WOMAC A (Pain) Subscale (see Patient Population and Demographics), performed by analysis of covariance (ANCOVA).

1.9.3 Patient Population and Demographics

Study patients had primary OA of the knee and were at least 40 years old. The diagnosis was confirmed via recent radiograph showing osteophyte(s) per American College of Rheumatology clinical plus radiographic criteria.5 Study patients had continued target knee pain despite use of conservative treatment and NSAIDs. Patients with severe disease (Grade IV) per Kellgren-Lawrence criteria, or who had prior arthroplasty in the target knee, were excluded. At the beginning of the study, subjects had moderate or severe target knee pain when walking on a flat surface (on a 5-point Likert scale where 0 = none, 1 = mild, 2 = moderate, 3 = severe, 4 = extreme), and an average score of 1.5 to 3.5 on the five questions of the WOMAC A Subscale. Patients were asked to rate their degree of pain when:

1. Walking on a flat surface
2. Going up and down stairs
3. Resting during the night
4. Sitting or lying
5. Standing upright

Table 1-2 summarizes the demographics and baseline characteristics. There were no clinically meaningful differences between treatment groups in any baseline parameter.

Table 1-2: Summary of Demographic and Baseline Characteristics

Parameter/Category	Synvisc-One (N=124)*	Placebo (N=129)*	Total (N=253)
Age, n *	124	129	253
Mean (SD)	63.6 (9.6)	62.5 (9.2)	63.0 (9.4)
Range	42, 83	43, 84	42, 84
Sex, n *	124	129	253
Female, n (%)	92 (74%)	88 (68%)	180 (71%)
Race, n *	124	129	253
Caucasian, n (%)	118 (95%)	125 (97%)	243 (96%)
Non-Caucasian, n (%)	6 (5%)	4 (3%)	10 (4%)
Body Mass Index (kg/m2), n *	123	129	252
Mean (SD)	29.1 (4.8)	29.8 (5.7)	29.4 (5.3)
Range	20.7, 46.0	19.5, 52.4	19.5, 52.4
Prior Corticosteroids In Target Knee, n **	123	130	253
Yes – n (%)	40 (32%)	31 (24%)	71 (28%)
Prior Arthroscopy In Target Knee, n **	123	130	253
Yes – n (%)	26 (21%)	28 (22%)	54 (21%)
Tibio-Femoral Joint Modified Kellgren-Lawrence Numerical Grading System **			
Grade II	63 (51%)	51 (39%)	114 (45%)
Grade III	60 (49%)	78 (60%)	138 (55%)
Grade IV	0	1 (1%)	1 (0%)
Total WOMAC Score (0-96); Mean (SD) *	55.1 (10.5)	54.8 (9.4)	
WOMAC A Score (0-4); Mean (SD) *	2.30 (0.43)	2.25 (0.41)	
PTGA -- Mean (SD) (0-4) *	2.57 (0.67)	2.50 (0.64)	
COGA -- Mean (SD) (0-4) *	2.44 (0.76)	2.49 (0.75)	

* ITT Population
** Safety Population

1.10 TREATMENT AND EVALUATION SCHEDULE

1.10.1 First Study Treatment

Patients were followed for 26 weeks. Study visits were scheduled for screening, baseline, and weeks 1, 4, 8, 12, 18 and 26. Test article was injected aseptically at the baseline visit after arthrocentesis to withdraw any effusion or synovial fluid present. Patients were not permitted to take NSAIDs (including cyclo-oxygenase II inhibitors), opioid analgesics or corticosteroids (by any route) during the study, but were permitted to take up to 4 g per day of acetaminophen as needed for "rescue" of target knee pain. "Rescue" medication was not permitted within 48 hours of any study visit. Target knee assessment, patient and clinician global assessments (PTGA & COGA), WOMAC and safety evaluations were performed at each study visit.

1.10.2 Repeat Study Treatment

If patients in either blinded treatment group had at least mild pain in the target knee at the week 26 visit (and had experienced no major safety concerns after the first treatment administration), they were offered an injection of (open-label) Synvisc-One. Those who chose to receive the second injection were followed for 4 weeks.

1.11 CLINICAL RESULTS

The primary efficacy endpoint for the study, the difference between the treatment groups in Change from Baseline over 26 Weeks in the WOMAC A Pain Score (Table 1-3) was met.

Table 1-3: Primary Efficacy Results: WOMAC A (Pain) Score Overall Change from Baseline Over 26 Weeks – ITT

	Baseline Mean (SE)	Mean Post-treatment (SE)	Estimated Change (SE)	Estimated Difference from Placebo (95% CI)	p-value (ANCOVA)
Synvisc (n=124)	2.30 (0.04)	1.43 (0.06)	-0.84 (0.06)	-0.15 (-0.30, -0.00)	0.047
Placebo (n=129)	2.25 (0.04)	1.59 (0.06)	-0.69 (0.06)		

Synvisc-One also demonstrated statistically significant superiority to placebo injection in multiple pre-defined secondary outcome measures. These included PTGA over 26

weeks, PTGA at 26 weeks, COGA over 26 weeks, COGA at 26 weeks, and pain while walking on a flat surface (WOMAC A1) both over 26 weeks and at 26 weeks (see Table 1-4, Table 1-5, and **Table 1-6**).

Table 1-4: Patient Global Assessments (PTGA) Overall and at Week 26 – ITT (Data Shown: Percentage of Patients Reporting Each Level of Assessment at Week 26)

	Week 26		Estimate of Odds Ratio (Placebo/Synvisc-One) (95% CI)	
	Synvisc-One	Placebo	At Week 26	Over 26 Weeks
Very Well	7.3%	1.6%	0.51 (0.31, 0.82) p = 0.005	0.69 (0.50, 0.96) p = 0.029
Well	26.6%	20.9%		
Fair	40.3%	41.9%		
Poor	16.9%	24.0%		
Very Poor	1.6%	2.3%		

Table 1-5: Clinical Observer Global Assessments (COGA) Overall and at Week 26 – ITT (Data Shown: Percentage of Patients Reporting Each Level of Assessment at Week 26)

	Week 26		Estimate of Odds Ratio (Placebo/Synvisc-One) (95% CI)	
	Synvisc-One	Placebo	At Week 26	Over 26 Weeks
Very Well	10.5%	6.2%	0.56 (0.34, 0.93) p = 0.025	0.71 (0.50, 0.99) p = 0.041
Well	29.8%	24.0%		
Fair	30.6%	29.5%		
Poor	17.7%	26.4%		
Very Poor	4.0%	4.7%		

The WOMAC A1 responder rate (where response was defined as 1 or more category change from baseline and the patient did not withdraw from the study) was significantly higher in the Synvisc group than in the control group. Seventy-one percent of the patients were responders at week 18 in the Synvisc group (versus 54% in the control group, p=0.003). At week 26, 64% of patients in the Synvisc group were responders, while only 50% of patients in the control group were responders (p=0.028).

Table 1-6: WOMAC A1 (Walking Pain) Overall and at Week 26 – ITT (Data Shown: Percentage of Patients Reporting Each Level of Pain at Week 26)

	Week 26		Estimate of Odds Ratio (Placebo/Synvisc-One) (95% CI)	
	Synvisc-One	Placebo	At Week 26	Over 26 Weeks
None	13.7%	10.1%	0.56	0.64
Mild	36.3%	30.2%	(0.35, 0.92)	(0.45, 0.91)
Moderate	33.1%	32.6%		
Severe	8.9%	14.7%	p = 0.022	p = 0.013
Extreme	0.8%	3.1%		

There were non-statistically significant differences favoring Synvisc-One in the variables, WOMAC C (Physical Function) Change from Baseline at Week 26, WOMAC A Responder Analysis and OMERACT-OARSI Responder Analysis (at Week 26 and over 26 weeks). There were no significant differences between treatment arms in Total WOMAC Score or WOMAC B (Stiffness). There was no significant difference between treatment arms in use of rescue medication.

1.12 CONCLUSIONS DRAWN FROM THE STUDIES

This double-blind, placebo-controlled study demonstrated that a single injection of 6 ml of hylan G-F 20 is safe and effective in providing symptomatic relief up to 26 weeks in patients with primary knee OA.

There was a statistically significant estimated treatment difference (-0.15, p=0.047) between the 2 treatment groups for the primary efficacy endpoint of this study, the change from Baseline over the course of the 26-week study using the patient's assessment of his/her pain (WOMAC LK 3.1 A).

Overall, this study confirms a favorable risk/benefit profile of a single injection of 6 ml of Synvisc in patients with symptomatic primary OA of the knee;

- A statistically significant improvement in the primary efficacy endpoint, WOMAC LK 3.1 A Pain Score (overall change from Baseline) in patients treated with Synvisc compared to saline control.

- Statistically significant improvement in WOMAC LK 3.1 A1 (Walking Pain) subscores (overall and at Week 26) for patients in the ITT Population treated with Synvisc compared to saline control.

- Statistically significant improvements in the PTGA (overall and at Week 26) for patients in the ITT Population treated with Synvisc compared to saline control.

- Statistically significant improvements in the COGA (overall and at Week 26) for patients in the ITT Population treated with Synvisc compared to saline control.

- Higher OMERACT-OARSI responder rate (overall and at Week 26) in patients treated with Synvisc compared to saline control that approached statistical significance.

- A similar safety profile for Synvisc and saline control. No new unrecognized AE(s) were identified with 1 injection of 6 ml of Synvisc during this study as compared to the current label.

- The safety profile from the Initial Treatment Phase of the study was confirmed during the Repeat Treatment Phase of the study, indicating no increase of AEs in the patients receiving a second 6 ml injection of Synvisc.

1.13 PANEL RECOMMENDATIONS

To be completed by FDA.

1.14 CDRH DECISION

To be completed by FDA.

1.15 APPROVAL SPECIFICATION

Directions for Use: See product labeling.

Post-approval Requirement and Restrictions: See approval order.

1.16 REFERENCES

1. Synvisc® Package Insert

2. Conrozier T, Schulz A, Beks P, et al., Prospective, multi-centre, randomised evaluation of the safety and efficacy of five dosing regimens of viscosupplementation with hylan G-F 20 in patients with symptomatic tibio-femoral osteoarthritis. Osteoarthritis Cartilage 2005;13 (Suppl 1);S93.

3. Chevalier X, Jerosch J, Luyten FP, et al., A double-blind, randomized, placebo-controlled evaluation of the efficacy and safety of a single dose of 6 ml of hylan G-F 20 in patients with symptomatic osteoarthritis of the knee. Ann Rheum Dis 2007;66 (Suppl 2).

4. Bellamy N, Watson Buchanan W, Goldsmith CH, et al., Validation study of WOMAC: A health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. J Rheumatol 1988;15:1833-1840.

5. Altman R, Asch E, Bloch D, et al., Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the knee. Arthritis Rheum 1986;29:1039-1049.