

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

### 3 **DESCRIPTION**

4 Synvisc-One™ (hylan G-F 20) is an elastoviscous fluid containing hylan polymers produced from  
5 chicken combs. Hylans are derivatives of hyaluronan (sodium hyaluronate), a natural complex  
6 sugar of the glycosaminoglycan family. Hyaluronan is a long-chain polymer containing repeating  
7 disaccharide units of Na-glucuronate-N-acetylglucosamine.

### 8 **INDICATIONS**

9 Synvisc-One is indicated for the treatment of pain in osteoarthritis (OA) of the knee in patients  
10 who have failed to respond adequately to conservative nonpharmacologic therapy and simple  
11 analgesics, e.g., acetaminophen.

### 12 **CONTRAINDICATIONS**

- 13 • Do not administer to patients with known hypersensitivity (allergy) to hyaluronan (sodium  
14 hyaluronate) preparations.
- 15 • Do not inject Synvisc-One in the knees of patients having knee joint infections or skin diseases  
16 or infections in the area of the injection site.

### 17 **WARNINGS**

- 18 • Do not concomitantly use disinfectants containing quaternary ammonium salts for skin  
19 preparation because hyaluronan can precipitate in their presence.
  - 20 • Do not inject Synvisc-One extra-articularly or into the synovial tissues and capsule.
- 21 Intravascular injections of Synvisc-One may cause systemic adverse events.

### 22 **PRECAUTIONS**

#### 23 General

- 24 • The safety and efficacy of Synvisc-One in locations other than the knee and for conditions other  
25 than osteoarthritis have not been established.
- 26 • Injection of anesthetics or other medications into the knee joint during Synvisc-One therapy  
27 may be performed up to a 3:1 ratio (Synvisc-One: medication) without affecting the visco-elastic

28 properties of Synvisc-One. The safety and efficacy of intra-articular administration of Synvisc-One  
29 concurrently with other medications have not been established.

- 30 • Use caution when injecting Synvisc-One into patients who are allergic to avian proteins,  
31 feathers or egg products.
- 32 • The safety and efficacy of Synvisc-One in severely inflamed knee joints have not been  
33 established.
- 34 • Strict aseptic administration technique must be followed.
- 35 • **STERILE CONTENTS.** The syringe is intended for single use. The contents of the syringe must  
36 be used immediately after its packaging is opened. Discard any unused Synvisc-One.
- 37 • Do not use Synvisc-One if package is opened or damaged. Store in original packaging  
38 (protected from light) at room temperature below 86° F (30° C). **DO NOT FREEZE.**
- 39 • Remove any synovial fluid or effusion before injecting Synvisc-One.
- 40 • Synvisc-One should be used with caution when there is evidence of lymphatic or venous stasis in  
41 the leg to be injected.

#### 42 **Information for Patients**

- 43 • Provide patients with a copy of the Patient Labeling prior to use.
- 44 • Mild to moderate pain, swelling and/or effusion of the injected knee have been reported in  
45 clinical trials that were related to intra-articular injection of Synvisc-One. These events were  
46 typically transient and usually resolved on their own or with conservative treatment.
- 47 • As with any invasive joint procedure, it is recommended that the patient avoid strenuous  
48 activities (for example, high impact sports such as soccer, tennis or jogging) or prolonged weight-  
49 bearing activities for approximately 48 hours following the intra-articular injection. The patient  
50 should consult his or her physician regarding the appropriate time to resume such activities.

#### 51 **Use in Specific Populations**

- 52 • **Pregnancy:** The safety and effectiveness of Synvisc-One have not been established in  
53 pregnant women.

54 • **Nursing mothers:** It is not known if Synvisc-One is excreted in human milk. The safety and  
55 effectiveness of Synvisc-One have not been established in lactating women.

56 • **Children:** The safety and effectiveness of Synvisc-One have not been established in children.

## 57 **ADVERSE EVENTS**

### 58 **Adverse Events Involving the Injected Knee**

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

63 **Initial Treatment Phase:** The overall proportion of patients with AEs irrespective of treatment  
64 relatedness (Synvisc-One: n=70, 56.9%; Placebo: n=79, 60.8%) and with target knee AEs  
65 (Synvisc-One: n=44, 35.8%; Placebo: n=44, 33.8%) was comparable between the two treatment  
66 groups. There were 7 (5.7%) patients in the Synvisc-One group and 5 (3.8%) patients in the  
67 Placebo group who experienced AEs assessed as related to the study injection. There were 4  
68 (3.3%) patients in the Synvisc-One group and 2 (1.5%) patients in the Placebo group who  
69 experienced AEs assessed as related to the study treatment.

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71 **Patients with Adverse Events in the Injected Knee**

<b>MedDRA Preferred Term</b>	<b>Synvisc-One</b> N=123 n (%)	<b>Placebo</b> N=130 n (%)	<b>Total</b> 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%)

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

74

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

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

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

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

88 patients with Treatment Emergent AEs was Synvisc-One/ Synvisc-One: n=9, 11.7% and Placebo/  
89 Synvisc-One: n=13, 15.7%.

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

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

98 **Overall Target Knee Safety Summary:** The safety profile of Synvisc-One is similar to the  
99 Clinical and Post-marketing experience seen with Synvisc® where pain, swelling and effusion  
100 were the most frequently occurring AEs in the injected knee. There have been post market  
101 reports for Synvisc indicating that in some cases the joint effusion may be large and can cause  
102 pronounced pain; it is important to remove and to analyze the fluid to rule out infection or  
103 crystalline arthropathies. These types of severe AEs were not observed in either the initial or  
104 repeat treatment phase of the Synvisc-One trial. IA infections did not occur in any of the clinical  
105 trials of Synvisc/ Synvisc-One and have been reported only rarely during clinical use of Synvisc.  
106

#### 107 **Adverse Events Outside of the Target Knee**

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

113 Synvisc® post marketing experience has identified the following systemic events to occur rarely  
114 with administration: rash, hives, itching, fever, nausea, headache, dizziness, chills, muscle

115 cramps, paresthesia, peripheral edema, malaise, respiratory difficulties, flushing and facial  
116 swelling.

117 No new systemic AEs were identified during this study as compared to the systemic AEs  
118 identified with Synvisc®.<sup>1</sup>

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## 120 **CLINICAL STUDIES**

### 121 ***Pilot Study***

122 The treatment regimen for Synvisc-One was selected on the basis of a 100-patient pilot dose-  
123 ranging study in which three 2 ml doses (a total of 6 ml) of hylan G-F 20 delivered in one injection  
124 had preliminary efficacy trends similar to three 2 ml doses delivered in three injections over three  
125 weeks, and equal to or better than preliminary efficacy trends of several other dosing schedules  
126 tested.<sup>1</sup>

### 127 ***Pivotal Clinical Trial***

128 Study Design: The safety and efficacy of Synvisc-One were investigated in a prospective, well-  
129 controlled randomized double-blind, 2-arm (parallel group) clinical trial.<sup>2</sup> A total of 253 patients  
130 were randomly assigned to study treatment at 21 sites in 6 countries; 123 received 6 mL of  
131 Synvisc-One and 130 received 6 mL of placebo (buffered saline solution). Neither the patients  
132 nor the clinical observers knew the patients' treatment allocations. The outcome measures  
133 collected included the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC;  
134 LK 3.1 A version)<sup>3</sup>, patient global assessment (PTGA), clinical observer global assessment  
135 (COGA), and use of rescue analgesic (see Treatment and Evaluation Schedule). The primary  
136 patient population analyzed was intent-to-treat (ITT). The primary efficacy analysis was a  
137 comparison over 26 weeks between the two treatment groups of change from baseline in the  
138 WOMAC A (Pain) Subscale (see Patient Population and Demographics), performed by analysis  
139 of covariance (ANCOVA).

### 140 **Patient Population and Demographics**

141 Study patients had primary osteoarthritis of the knee and were at least 40 years old. The  
142 diagnosis was confirmed via recent radiograph showing osteophyte(s) per American College of

143 Rheumatology clinical plus radiographic criteria.<sup>4</sup> Study patients had continued target knee pain  
144 despite use of conservative treatment and analgesics/non-steroidal anti-inflammatory drugs  
145 (NSAIDs). Patients with severe disease (Grade IV) per Kellgren-Lawrence criteria, or who had  
146 prior arthroplasty in the target knee, were excluded. At the beginning of the study, subjects had  
147 moderate or severe target knee pain when walking on a flat surface (on a 5-point Likert scale  
148 where 0 = none, 1 = mild, 2 = moderate, 3 = severe, 4 = extreme), and an average score of 1.5 to  
149 3.5 on the five questions of the WOMAC A Subscale. Patients were asked to rate their degree of  
150 pain when:

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

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

158 **Table 1. 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/m <sup>2</sup> ), 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)	
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\* ITT Population

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\*\* Safety Population

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**Treatment and Evaluation Schedule**

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*First Study Treatment*

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Patients were followed for 26 weeks. Study visits were scheduled for screening, baseline, and

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weeks 1, 4, 8, 12, 18 and 26. Test article was injected aseptically at the baseline visit after

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arthrocentesis to withdraw any effusion or synovial fluid present. Patients were not permitted to

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take NSAIDs (including cyclo-oxygenase II inhibitors), opioid analgesics or corticosteroids (by any

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route) during the study, but were permitted to take up to 4 g per day of acetaminophen as needed

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for “rescue” of target knee pain. “Rescue” medication was not permitted within 48 hours of any

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study visit. Target knee assessment, patient and clinician global assessments (PTGA & COGA),

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WOMAC and safety evaluations were performed at each study visit.

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*Repeat Study Treatment*

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If patients in either blinded treatment group had at least mild pain in the target knee at the week

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26 visit (and had experienced no major safety concerns after the first treatment administration),

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they were offered an injection of (open-label) Synvisc-One. Those who chose to receive the

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second injection were followed for 4 weeks.

176

**Clinical Results**

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The primary endpoint for the study, the difference between the treatment groups in Change from

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Baseline over 26 Weeks in the WOMAC A Pain Score (Table 2) was met.

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180

**Table 2. Primary Efficacy Results: WOMAC A (Pain) Score Overall Change from Baseline**

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**Over 26 Weeks – ITT**

	<b>Baseline Mean (SE)</b>	<b>Mean Post- treatment (SE)</b>	<b>Estimated Change (SE)</b>	<b>Estimated Difference from Placebo (95% CI)</b>	<b>p-value (ANCOVA)</b>
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)		

182

183 Synvisc-One also demonstrated statistically significant superiority to placebo injection in multiple  
184 pre-defined secondary outcome measures. These included PTGA over 26 weeks, PTGA at 26  
185 weeks, COGA over 26 weeks, COGA at 26 weeks, and pain while walking on a flat surface  
186 (WOMAC A1) both over 26 weeks and at 26 weeks (see Tables 3-5).

187

188 **Table 3. Patient Global Assessments (PTGA) Overall and at Week 26 – ITT (Data Shown:**  
189 **Percentage of Patients Reporting Each Level of Assessment at Week 26)**

	<b>Week 26</b>		<b>Estimate of Odds Ratio (Placebo/Synvisc-One) (95% CI)</b>	
	<b>Synvisc-One</b>	<b>Placebo</b>	<b>At Week 26</b>	<b>Over 26 Weeks</b>
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%		

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191

192 **Table 4. Clinical Observer Global Assessments Overall and at Week 26 – ITT (Data Shown:**  
 193 **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%		

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195 The WOMAC A1 responder rate (where response was defined as 1 or more category  
 196 change from baseline and the patient did not withdraw from the study) was significantly  
 197 higher in the Synvisc group than in the control group. Seventy-one percent of the patients  
 198 were responders at week 18 in the Synvisc group (versus 54% in the control group,  
 199 p=0.003). At week 26, 64% of patients in the Synvisc group were responders, while only  
 200 50% of patients in the control group were responders (p=0.028).  
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202 **Table 5. WOMAC A1 (Walking Pain) Overall and at Week 26 – ITT (Data Shown:**  
 203 **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 (0.35, 0.92)  p = 0.022	0.64 (0.45, 0.91)  p = 0.013
Mild	36.3%	30.2%		
Moderate	33.1%	32.6%		
Severe	8.9%	14.7%		
Extreme	0.8%	3.1%		

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205

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

## 212 **DETAILED DEVICE DESCRIPTION**

213 Synvisc-One contains three doses of hylan G-F 20 which consists of hylan A (average molecular  
214 weight 6,000,000 daltons) and hylan B hydrated gel in a buffered physiological sodium chloride  
215 solution, pH 7.2. Synvisc-One has an elasticity (storage modulus  $G'$ ) at 2.5 Hz of  $111 \pm 13$   
216 Pascals (Pa) and a viscosity (loss modulus  $G''$ ) of  
217  $25 \pm 2$  Pa (elasticity and viscosity of knee synovial fluid of 18 to 27- year-old humans measured  
218 with a comparable method at 2.5 Hz:  $G' = 117 \pm 13$  Pa;  $G'' = 45 \pm 8$  Pa.)

219 Each syringe of Synvisc-One contains three doses of hylan G-F 20:

220 Hylan polymers (hylan A + hylan B) 48 mg

221 Sodium chloride 51 mg

222 Disodium hydrogen phosphate 0.96 mg

223 Sodium dihydrogen phosphate monohydrate 0.24 mg

224 Water for injection q.s. to 6.0 ml

## 225 **HOW SUPPLIED**

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

## 228 **DIRECTIONS FOR USE**

229 Synvisc-One is administered as a single intra-articular injection.

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

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

234 Precaution: Strict aseptic administration technique must be followed.

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

237 Precaution: Remove synovial fluid or effusion before injecting Synvisc-One.

238 Do not use the same syringe for removing synovial fluid and for injecting Synvisc-One, but the  
239 same needle should be used. Take particular care to remove the tip cap of the syringe and  
240 needle aseptically. Inject Synvisc-One into the knee joint through an 18 to 20 gauge needle. To  
241 ensure a tight seal and prevent leakage during administration, secure the needle tightly while  
242 firmly holding the luer hub.

243 Precaution: Do not over tighten or apply excessive leverage when attaching the needle or  
244 removing the needle guard, as this may break the tip of the syringe. Injection of anesthetics or  
245 other medications into the knee joint during Synvisc-One therapy may be performed up to a 3 :1  
246 ratio (Synvisc: medication) without affecting the characteristics of the product.

247 Precaution: The syringe containing Synvisc-One is intended for single use. The contents of the  
248 syringe must be used immediately after the syringe has been removed from its packaging. Inject  
249 the full 6 ml in one knee only. If treatment is bilateral, a separate syringe must be used for each  
250 knee. Discard any unused Synvisc-One.

251 **MANUFACTURED AND DISTRIBUTED BY:**

252 Genzyme Biosurgery a division of Genzyme Corporation

253 1125 Pleasant View Terrace

254 Ridgefield, New Jersey 07657

255 Telephone: 1-888-3-SYNVISC (1-888-379-6847)

256 Covered by U.S. patents #4,636,524, #4,713,448, #5,099,013, #5,143,724.

257 SYNVISIC-ONE™ and GENZYME are registered trademarks of Genzyme Corporation.

258 **REFERENCES**

- 259 1. Synvisc® Package Insert
- 260 2. Conrozier T., Schulz A., Beks P., et al., Prospective, multi-centre, randomised evaluation of  
261 the safety and efficacy of five dosing regimens of viscosupplementation with hylan G-F 20 in

- 262 patients with symptomatic tibio-femoral osteoarthritis. *Osteoarthritis Cartilage* 2005;13 (Suppl  
263 1);S93.
- 264 3. Chevalier X., Jerosch J., Luyten FP., et al., A double-blind, randomized, placebo-controlled  
265 evaluation of the efficacy and safety of a single dose of 6 ml of hylan G-F 20 in patients with  
266 symptomatic osteoarthritis of the knee. *Ann Rheum Dis* 2007;66 (Suppl 2).
- 267 4. Bellamy N., Watson Buchanan W., Goldsmith CH., et al., Validation study of WOMAC: A  
268 health status instrument for measuring clinically important patient relevant outcomes to  
269 antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. *J Rheumatol*  
270 1988;15:1833-1840.
- 271 5. Altman R, Asch E, Bloch D, et al., Development of criteria for the classification and reporting  
272 of osteoarthritis. Classification of osteoarthritis of the knee. *Arthritis Rheum* 1986;29:1039-  
273 1049.

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

277 **WHAT IS SYNVISC-ONE™?**

278 Synvisc-One is a gel-like mixture that is made up of hylan A fluid, hylan B gel, and salt water.  
279 Hylan A and hylan B are made from a substance called hyaluronan (pronounced hy-al-u-ROE-  
280 nan), also known as sodium hyaluronate that comes from rooster combs. This is a natural  
281 substance found in the body and is present in very high amounts in joints. The body's own  
282 hyaluronan acts like a lubricant and a shock absorber in the joint and is needed for the joint to  
283 work properly. Osteoarthritis (pronounced OS-te-o-arth-RI-tis) (OA) is a type of arthritis that  
284 involves the wearing down of cartilage (the protective covering on the ends of your bones). In OA,  
285 there may not be enough hyaluronan, and there may be a decrease in the quality of the  
286 hyaluronan in the joint. Synvisc-One comes in a syringe containing 6 mL (1 ¼ teaspoon) of  
287 product. Synvisc-One is injected directly into your knee.

288 **WHAT IS SYNVISC-ONE USED FOR?**

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

291 **WHAT ARE THE BENEFITS OF SYNVISC-ONE?**

292 As shown in a medical study of 253 patients with osteoarthritis (OA) of the knee, the major  
293 benefits of Synvisc-One are pain relief and improvement in other symptoms related to OA of the  
294 knee. Patients in the study got pain relief starting 1 month after the injection of Synvisc-One that  
295 lasted 6 months.

296 The study was conducted in 6 countries with 21 physicians. The patients in the study had knee  
297 OA that was not end-stage, had moderate to severe pain, and did not have sufficient relief of their  
298 pain and symptoms with medications taken by mouth.

299 Patients in the study were assigned by chance to receive either a single injection of Synvisc-One,  
300 or an injection of the same volume of salt water (a "placebo" injection). Neither the patients nor  
301 the doctors evaluating them knew which treatment they received. Any fluid that was present in

302 the patient's knee was removed before the injection. The patients were seen by their doctor at  
303 standard times over 6 months. Information was collected about how much pain they were  
304 experiencing doing various types of activities, how much they were limited in their daily activities  
305 by their OA, and on their overall condition. Their doctor also provided an overall rating of their OA.  
306 The main measure of the study was how much pain the subjects had doing five common types of  
307 activities over the 6 months of the study. Daily activity limitations and overall evaluations were  
308 also compared between the group of patients receiving Synvisc-One injection and the group  
309 receiving salt water injection. The study showed that patients receiving Synvisc-One had  
310 significantly less pain over 6 months, and significantly better overall assessments, than the  
311 patients who received the salt water injections.

### 312 **WHAT OTHER TREATMENTS ARE AVAILABLE FOR OA?**

313 If you have OA, there are other things you can do besides getting Synvisc-One. These include:

#### 314 **Non-drug treatments**

- 315 • avoiding activities that cause knee pain
- 316 • exercise
- 317 • physical therapy
- 318 • removal of excess fluid from your knee

#### 319 **Drug therapy**

- 320 • pain relievers such as acetaminophen and narcotics
- 321 • drugs that reduce inflammation (signs of inflammation are swelling, pain or redness), such as  
322 aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen and naproxen
- 323 • steroids that are injected directly into your knee

### 324 **ARE THERE ANY REASONS WHY YOU SHOULD NOT RECEIVE SYNVISC-ONE?**

- 325 • You should not get this product if you have had any allergic reaction before to Synvisc-One or  
326 any hyaluronan-based products. Signs of an allergic reaction may include swelling of your face,  
327 tongue, or throat; difficulty breathing or swallowing; shortness of breath; wheezing; chest pain; a  
328 tightness in your throat; sleepiness; rash; itching; hives; flushing; and/or fever. You should call  
329 your doctor immediately if you develop any of these signs of an allergic reaction.

330 • You should not be given Synvisc-One if you have a knee joint infection or skin diseases or  
331 infections around the area where the injection will be given, or circulatory problems in your legs.  
332 Talk to your doctor if you have any questions about this information.

333 **THINGS YOU SHOULD KNOW ABOUT SYNVISC-ONE:**

- 334 • Synvisc-One is only for injection into the knee, performed by a doctor or other qualified health  
335 care professional.
- 336 • Tell your doctor if you are allergic to products from birds such as feathers, eggs, and poultry.
- 337 • Inform your doctor if you have significant swelling or blot clots in the leg. After you receive the  
338 injection, you may need to avoid activities such as jogging, tennis, heavy lifting, or standing for a  
339 long time.
- 340 • Synvisc-One has not been tested in pregnant women, or women who are nursing. You should  
341 tell your doctor if you think you are pregnant, or if you are nursing a child.
- 342 • The safety and effectiveness of Synvisc-One have not been tested in children.

343 **POSSIBLE SIDE EFFECTS:**

- 344 • The side effects (also called reactions) sometimes seen after an injection were pain, swelling,  
345 heat, redness, and/or fluid build-up around the knee. These reactions were generally mild and did  
346 not last long; cases where the swelling is extensive and painful should be discussed with your  
347 doctor. • These reactions are generally treated by giving pain relievers by mouth such as  
348 acetaminophen or by giving NSAIDs by mouth or injections of steroids, or by removing fluid from  
349 the knee joint. Patients have rarely undergone  
350 arthroscopy (a surgical inspection of the knee joint) and other medical procedures.
- 351 • Rare cases of knee joint infection have been reported after Synvisc® injections.
- 352 • Rashes, hives and itching have been seen in patients after Synvisc® treatment. Before you are  
353 given Synvisc-One, tell your doctor if something like this has ever happened to you after receiving  
354 an injection of Synvisc® or any other hyaluronan products.
- 355 • Other less common side effects seen with Synvisc® have been: muscle pain/cramps, flushing  
356 and/or swelling of your face, fast heartbeat, nausea (or feeling sick to your stomach), dizziness,  
357 fever, chills, headache, difficulty breathing, swelling in your arms and/or legs, prickly feeling of

358 your skin, and in rare cases a low number of platelets in the blood (platelets are a type of blood  
359 cell that are needed to help clot your blood when you are cut or injured).

360 • If any of the above symptoms or signs appear after you are given Synvisc-One, or if you have  
361 any other problems, you should call your doctor.

362 **HOW IS SYNVISC-ONE GIVEN?**

363 Your doctor will give one injection of Synvisc-One (6mL) into your knee.

364 **MANUFACTURED AND DISTRIBUTED BY:**

365 Genzyme Biosurgery

366 a division of Genzyme Corporation

367 1125 Pleasant View Terrace

368 Ridgefield, New Jersey 07657

369 **HOW DO I GET MORE INFORMATION ABOUT SYNVISC?**

370 If you have any questions or would like to find out more about Synvisc-One, you may call

371 Genzyme Biosurgery at 1-888-3-SYNVISC (1-888-379-6847). SYNVISC, SYNVISC-ONE and

372 GENZYME are registered trademarks of Genzyme Corporation.