IFU Synvisc-One
India
Side 1
Material No. 639441
**Rev. 29 JUN 2016**

# Hylan Polymer A & B G-F 20 Prefilled Syringe 8mg/ml

SYNVISC ONE®

Net content: 6 mL

For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory

This package insert is continually updated.
Please read carefully before using a new pack.

639441

**Synvisc-One® (Hylan G-F 20)/(Hylan Polymer A & B G-F 20)**

Synvisc-One is supplied in a 10-ml glass syringe containing 6 ml hylan G-F 20.

**COMPOSITION**
Content per ml (hylan G-F 20):
Each 1 ml contains: hylan polymer 8.0 mg, sodium chloride 8.5 mg, disodium hydrogen phosphate 0.16 mg, sodium dihydrogen phosphate hydrate 0.04 mg, water for injection q.s.

**INDICATION**
Hylan G-F 20 (Synvisc-One) is indicated:

- For the treatment of pain in osteoarthritis of the knee in patients who have failed to respond adequately to conservative non pharmacologic therapy and to simple analgesics.

- For the treatment to decrease pain & discomfort allowing more extensive movement of the Knee

The safety and efficacy of Synvisc-One for conditions other than osteoarthritis has not been established.

The safety and effectiveness of the use of Synvisc-One concomitantly with other intra-articular injectables has not been established.

**DOSAGE FORM**
Synvisc-One is supplied in a 10-ml glass syringe containing 6 mL hylan G-F 20. The contents of the syringes are sterile and non-pyrogenic.
Synvisc-One should be administered under the supervision of a qualified physician or properly licensed practitioner.
Synvisc-One is administered intra-articularly according to the instructions given below.

Synvisc-One is administered as a single intra-articular injection.
Strict aseptic administration technique must be followed. Using an 18 to 20-gauge needle, remove synovial fluid or effusion before injecting Synvisc-One.
Do not use the same syringe for removing synovial fluid and for injecting Synvisc-One; however, the same 18 to 20-gauge needle should be used. Twist the tip cap before pulling it off, as this will minimize product leakage. To ensure a tight seal and prevent leakage during administration, secure the needle tightly while firmly holding the luer hub.
Precaution: Do not over tighten or apply excessive leverage when attaching the needle or removing the needle guard, as this may break the syringe tip.
Inject the full 6 ml in one knee only.

**DOSAGE AND ADMINISTRATION**
- Remove synovial fluid or effusion before injecting hylan G-F 20 (Synvisc-One).
- Do not use hylan G-F 20 (Synvisc-One) if package is opened or damaged.
- Inject at room temperature.
- To remove the syringe from the blister (or tray), take hold of the syringe by the body, without touching the plunger rod.
- Administer using strict aseptic procedures, taking particular care when removing the tip cap.
- Twist the grey tip cap before pulling it off, as this will minimize product leakage
- Use an appropriate size of needle:
- Depending on the joint to be treated use the appropriate length of needle.
- Synvisc-One – 18 to 20-gauge
- To ensure a tight seal and prevent leakage during administration secure the needle tightly while firmly holding the Luer hub.
- Do not 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 re-sterilize hylan G-F 20 (Synvisc-One)
- Inject into the synovial space only.
- The syringe contents are for single use only. The contents of the syringe must be used immediately after the syringe has been removed from its packaging.
- When using fluoroscopic guidance, ionic or non-ionic contrast agent may be utilized. No more than 1 ml of contrast agent should be used per 2 ml of hylan G-F 20 (Synvisc One).

**CONTRAINDICATIONS**
Synvisc-One should not be used in patients with known hypersensitivity (allergy) to hyaluronan (sodium hyaluronate) preparations.
Synvisc-One should not be injected into the joint if there is venous or lymphatic stasis in the limb to be injected.
Synvisc-One should not be used in infected or severely inflamed joints or in patients having skin disease or infections in the area of the injection site.

**WARNINGS AND PRECAUTIONS FOR USE**
Do not inject Synvisc-One intravascularly. Intravascular injections may cause systemic adverse events.
Do not inject Synvisc-One extra-articularly or into the synovial tissues and capsule. Adverse events, generally in the area of the injection, have occurred following extra-articular injection of Synvisc-One.
Do not concomitantly use disinfectants containing quaternary ammonium salts for skin preparation because hyaluronan can precipitate in their presence.
Remove any synovial fluid or effusion prior to injecting Synvisc-One.
As with any invasive joint procedure, it is recommended that the patient avoid any strenuous activities for approximately 48 hours following the intra-articular injection, and resume full activities within a few days.
Synvisc-One have not been tested in pregnant women or children ≤ 21 year of age.
Synvisc-One contains small amounts of avian protein and should not be used in patients with related hypersensitivities.

**GENERAL**
The safety and efficacy of Synvisc-One for conditions other than osteoarthritis have not been established.
Synvisc-One is only intended for intra-articular use by a physician to treat pain associated with osteoarthritis of the knee.
The safety and effectiveness of the use of Synvisc-One concomitantly with other intra-articular injectables have not been established.

**USEFUL LABORATORY TESTS FOR MONITORING PATIENTS**
Not applicable.

**EFFECTS ON ABILITY TO DRIVE AND HANDLE HEAVY MACHINERY**
Not applicable.

**INTERACTIONS**
The company has not tested for interactions with other medicinal products, food, or laboratory tests or pharmaceutical incompatibilities when used as directed.

**DRUG/DRUG**
Not applicable.

**DRUG/FOOD**
Not applicable.

**PHARMACEUTICAL INCOMPATIBILITIES**
Synvisc-One should not be mixed with other medicinal products.

**DRUG/LABORATORY TESTS**
Not applicable.

**PREGNANCY AND LACTATION**
The safety and effectiveness of Synvisc-One has not been established in pregnant women. It is not known if Synvisc-One is excreted in human milk. The safety and effectiveness of Synvisc-One have not been established in lactating women.

**ADVERSE EVENTS**
Adverse events (and corresponding Preferred Terms- PTs) involving the injected joint that may occur after intra-articular injections of Synvisc-One are:
- Transient pain [PT-Arthralgia] and/or
- Transient swelling [PT-Joint swelling] and/or
- Effusion [PT-Joint effusion]

In worldwide post market experience, injection site reactions have been reported following an intra-articular injection of Synvisc-One.

**Injection site definition:**
Injection site encompasses the point of dermal entry to the site of the intended intra-articular deposition of Synvisc-One. The injection site will refer to dermis and surrounding tissue, the track of the needle and area of product administration.

Injection site events include:
- Injection site reaction [PT – Injection Site Reaction]
- Injection site pain/tenderness [PT – Injection Site Pain]
- Injection site bruising [PT – Injection Site Haematoma]
- Injection site swelling [PT – Injection Site Swelling]
- Injection site bleeding [PT – Injection Site Haemorrhage]
- Injection site itching [PT – Injection Site Pruritus]
- Injection site redness [PT – Injection Site Erythema]
- Injection site rash [PT – Injection Site Rash]
- Injection site warmth [PT-Injection Site Warmth]

**POSTMARKETING ADVERSE REACTIONS:**
Hypersensitivity reactions including anaphylactic reaction, anaphylactoid reaction, anaphylactic shock and angioedema have been reported.

Cases of acute inflammation , characterized by joint pain, swelling, effusion and sometimes joint warmth and/or stiffness, have been reported following an intra-articular injection of Synvisc-One. Analysis of synovial fluid reveals aseptic fluid with no crystals. This reaction often responds to Non Steoridal Anti Inflammatory Drugs (NSAIDS), intra-articular steroids and/or arthrocentesis.
Clinical benefit from the treatment may still be apparent after such reactions.

**OVERDOSE**
Not applicable when used as directed.

**DRUG ABUSE AND DEPENDENCE**
Not applicable.

**CLINICAL PHARMACOLOGY**

**NON-CLINICAL**
The material of Synvisc-One is the identical hylan G-F 20 which is supplied in a 10 ml glass syringe (Synvisc-One). The manufacturing process for hylan G-F 20 material has remained unchanged.

Safety testing for hylan G-F 20 was originally conducted under tripartite biocompatibility guidance for medical devices. This guidance was superseded by FDA Blue Book Memorandum #G95-1 and ISO 10993 guidance. All non-clinical and animal testing conducted on Synvisc is applicable to Synvisc-One:
The current ISO 10993 guidance classifies hylan G-F 20 as a tissue/bone contacting device with prolonged (>24 hours to 30 days) contact duration. The safety testing requirements for this classification include:
- Cytotoxicity
- Sensitization
- Genotoxicity
- Implantation

All of these tests were conducted on the final product and were found to meet the requirements of the tests.

The clearance of Synvisc and its gel and fluid components from the rabbit knee joint were determined. The test animals for these studies were New Zealand White rabbits weighting between 2.5 and 3.5 kg. The radiolabeled hylan material was administered as a single intra-articular injection of 0.3 ml. On a body weight basis, the test article was administered at a dose of 0.086 ml/kg. This is the same dose level expected to be delivered from a single 6 ml administration of Synvisc-One to a 70 kg individual. The gel component of Synvisc is the longer half-life moiety. In these studies, the apparent gel half-life was determined to be between 7.7 and 8.8 days. The apparent fluid half-life was determined to be between 1.2 and 1.5 days.

**Cytotoxicity**
BXR 45204-F, In Vitro Cytotoxicity Study (Agarose Overlay Method) in the L-929 Mouse Connective Tissue Cell Line [Hylan G-F 20]
**Sensitization**
BXR 45206-F, Delayed Contact Sensitization Study (A Maximization Method) in the Guinea Pig [Hylan G-F 20]

**Genotoxicity**
BXR 42226-F, Evaluation of a Test Article in the Salmonella typhimurium/Escherichia coli Plate Incorporation Mutagenesis Assay in the Presence and Absence of Aroclor-induced Rat Liver S-9 [Hylan G-F 20]
BXR 42231-F, Test for Chemical Induction of Chromosome Aberration in Cultured Chinese Hamster Ovary (CHO) Cells with and Without Metabolic Activation [Hylan G-F 20]
BXR 42225-F, Test for Chemical Induction of Gene Mutation at the HGPRT Locus in Cultured Chinese Hamster Ovary (CHO) Cells with and Without Metabolic Activation with Hylan G-F 20
BXR 42227-F, Test for Chemical Induction of Unscheduled DNA Synthesis in Rat Primary Hepatocytes Obtained from Rats Treated In Vivo with Hylan G-F 20
**Implantation**
BXR 45201-F, USP Muscle Implantation (with Histopathology) in the Rabbit (7 day) [Hylan G-F 20]
BXR 45202-F, USP Muscle Implantation (with Histopathology) in the Rabbit (30 day) [Hylan G-F 20]
**Clearance**
BXR 15211-F, Clearance of Hylan Fluid after Intra-articular Injection into Rabbit Knees, as Determined by Radiotracer Studies
BXR 25211-F, Clearance of Hydrated Hylan Gel after Intra-articular
injection into Rabbit Knees, as Determined by Radiotracer Studies
BXR 55211-F, Clearance of Hylan G-F 20 after Intra-articular injection into Rabbit Knees, as Determined by Radiotracer Studies

**CLINICAL TRIALS**
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.

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. 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.

A second study conducted at a single center in Germany was a concurrently controlled, randomized, double-blind prospective clinical trial with two treatment groups. This study compared the safety and effectiveness over a 26-week period of three weekly intra-articular injections of Synvisc and of physiological saline in 29 subjects (29 knees) with osteoarthritis of the knee. The results of the study were similar to those in the German multicenter study, except that the significance levels in most comparisons were smaller. 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.

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 contra-lateral 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.
To determine the safety and effectiveness of a single injection regimen of Synvisc-One in the reduction of the pain score in osteoarthritis of the knee, a prospective, randomized, double-blind, 2-arm (parallel group) clinical trial in 21 centers in six European countries was conducted. A total of 253 patients were randomly assigned to study treatment; 123 received 6 mL of Synvisc-One and 130 received 6 mL of Phosphate-Buffered Saline. Neither the patients nor the clinical observers knew the patients' treatment allocations. The outcome measures collected included the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC; Likert 3.1 A version), patient global assessment (PTGA), clinical observer global assessment (COGA), and use of rescue analgesic (see Treatment and Evaluation Schedule).

The intent-to-treat (ITT) population (all patients randomized) was used for the primary analysis. 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).

**Patient Population and Demographics**
Study patients had primary osteoarthritis of the knee per American College of Rheumatology criteria and were at least 40 years old. The diagnosis was confirmed via recent radiograph showing at least one osteophyte in the target knee. Study patients had continued target knee pain despite use of conservative treatment and analgesics/non-steroidal anti-inflammatory drugs (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 (Pain) Subscale. The WOMAC A Subscale asks study subjects to rate their degree of pain when:
- Walking on a flat surface
- Going up and down stairs
- Resting during the night
- Sitting or lying
- Standing upright
- Initial Treatment Phase

Patients were followed for 26 weeks. Study visits were scheduled for screening, baseline, and weeks 1, 4, 8, 12, 18 and 26. Injections were performed aseptically at the baseline visit after arthrocentesis to withdraw any effusion or synovial fluid present. Patients were not permitted to take long-acting 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 injected knee pain. "Rescue" medication was not permitted within 48 hours of any study visit. Injected knee assessment, patient and clinician global assessments (PTGA & COGA), WOMAC and safety evaluations were performed at each study visit.

**Repeat Treatment Phase**
If patients in either blinded treatment group had at least mild pain in the injected knee at the week 26 visit (and did not experience any significant clinical 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 for safety only.
The primary endpoint for the study, the difference between the treatment groups in change from baseline over 26 Weeks in the WOMAC A Pain Score was met.
Synvisc-One also demonstrated superiority to saline control in multiple pre-defined secondary outcome measures, which included PTGA over and at 26 weeks, COGA over and at 26 weeks, and pain while walking on a flat surface (WOMAC A1) over and at 26 weeks.
The WOMAC A1 responder rate (where response was defined as a 1-or-more category improvement from baseline and the patient did not withdraw from the study) was significantly higher in the Synvisc-One group than in the saline control group. Seventy-one percent (71%) of the patients were responders at week 18 in the Synvisc-One group (versus 54% in the saline control group). At week 26, 64% of patients in the Synvisc-One group were responders, while only 50% of patients in the saline control group were responders.

**DURATION OF EFFECT**

Generally the duration of effect for those patients who respond to treatment has been reported up to 26 weeks, although shorter and longer periods have also been observed. However, prospective clinical data in knee osteoarthritis patients have shown benefit of treatment up to 52 weeks, following a single course of three Synvisc injections.

**Synvisc-One**
Prospective clinical trial data in knee osteoarthritis patients have shown a reduction in pain for up to 52 weeks following a single Synvisc-One injection as well as related improvements in stiffness and function.
Clinical data from a double-blind, randomized, controlled trial in knee OA patients have shown a statistically significant and clinically meaningful reduction in pain compared to placebo. A total of 253 patients were treated (124 received Synvisc-One and 129 received placebo). Over 26 weeks, patients receiving Synvisc-One demonstrated a mean percent change in pain from baseline of 36% while patients in the placebo group had a mean percent change in pain from baseline of 29%.

Additional prospective clinical data from two multi-center, open-label studies in knee OA patients have shown statistically significant improvements in pain relief compared to baseline for up to 52 weeks following a single administration of Synvisc-One.

In the first study, 394 patients that received Synvisc–One demonstrated a statistically significant change in the WOMAC A1 - pain on walking subscore (28±19.89 mm on 100 mm VAS) from baseline over Week 26. In addition, statistically significant changes from baseline in WOMAC A1, and WOMAC A, B and C scores were observed over all six observation time periods between week 1 and week 52, demonstrating improvement in pain on walking and pain (WOMAC A1 -32.7±19.95 mm; WOMAC A -25.77±22.047 mm), stiffness (WOMAC B -25.77±22.047 mm), and function (WOMAC C -25.72±19.449 mm) over 52 weeks.

In the second study, 571 patients that received Synvisc-One, demonstrated statistically significant improvement in pain over 26 weeks as measured by Verbal Pain Questionnaire (VPQ). The mean pain assessment improved from 3.20 at Baseline to 2.24 at 26 week visit, with 64.6% of patients achieving pain relief. Secondary endpoints demonstrated statistically significant improvement in VPQ scores at all observation time points from 1 week to 52 weeks, with mean VPQ scores declining from 3.20 at baseline to 2.26 at 52 week visit and 61.5% of patients achieving pain relief.

(Ref:- A multicenter, prospective observational study of the safety and efficacy of a single injection of 6ml hylan G-F 20 in patients with symptomatic osteoarthritis of the knee in Germany, Final report July 2011, D. Daniel, P. Kiencke, J. Kresimon, R. Rychlik
-A Multicenter, Prospective, Open Label Study of the Safety and Efficacy of 6mL Synvisc-One® (hylan G–F 20) in Indian Patients with Symptomatic Osteoarthritis of the Knee(s) after Initial and Repeat Treatment ,Study Number: SYNV03809,Clinical Study Report Date: 03 April 2012)

**HOW SUPPLIED**
Synvisc-One is supplied in a 10-ml glass syringe containing 6 mL Hylan G-F 20. The contents of the syringes are sterile and non-pyrogenic.

**Manufactured by:**
M/s. Genzyme Biosurgery,
A Division of Genzyme Corporation,
1125 Pleasant View Terrace,
Ridgefield, NJ 07657, USA

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