GEL-SYN™

PRODUCT INFORMATION

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

CONTENT

Each 1 mL of Gel-Syn contains:

Sodium Hyaluronate:	8.4 mg
Sodium Chloride:	8.5 mg
Sodium Phosphate, Dibasic:	0.16 mg
Sodium Phosphate, Monobasic:	0.045 mg
Water for Injection:	q.s. to 1.0 mL

DESCRIPTION

Gel-Syn is a sterile, buffered solution of highly purified sodium hyaluronate with a molecular weight of approximately 1100 kDa, obtained through fermentation of *Streptococci* of Lancefield groups A and C and chemically unmodified.

INDICATION

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

CONTRAINDICATIONS

- Do not administer to patients with known hypersensitivity (allergy) to sodium hyaluronate preparations.
- Do not inject Gel-Syn into 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 sodium hyaluronate can precipitate in their presence.
- Inject into the synovial space only. Do not inject by intravascular route.
- Do not inject outside the synovial space or into the synovial tissue or capsule. An extra-articular injection of the product can cause local adverse events.

PRECAUTIONS

General

- The safety and effectiveness of Gel-Syn in locations other than the knee, and for conditions other than osteoarthritis, 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. Do not re-sterilize the product.
- Do not use Gel-Syn if package is opened or damaged. Store in original packaging at 20° to 25°C (68° - 77°F). DO NOT FREEZE.

- Gel-Syn is sensitive to light, and should therefore be used immediately after removal from the carton box.
- Do not use Gel-Syn in case of severe intra-articular effusion.
- Remove synovial fluid or effusion before each Gel-Syn injection.
- Gel-Syn should be used with caution when there is evidence of lymphatic or venous stasis in the leg to be treated.

INSTRUCTION FOR PATIENTS

- Provide patients with a copy of the Patient Labeling prior to use.
- Transient pain, sensation of heat, reddening or swelling may occur at the injection site after intra-articular injection of Gel-Syn.
- 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 within 48 hours following the intra-articular injection.

USE IN SPECIFIC POPULATIONS

- **Pregnancy:** The safety and effectiveness of Gel-Syn have not been established in pregnant women.
- **Nursing Mothers:** It is not known if Gel-Syn is excreted in human milk. The safety and effectiveness of Gel-Syn have not been established in lactating women.
- **Children:** The safety and effectiveness of Gel-Syn have not been established in children.

ADVERSE REACTIONS

The most common adverse events related to Gel-Syn injection reported in the clinical study are the following:

- Injection site pain (0.5%)

All adverse events related to Gel-Syn injection reported in the clinical study are provided in the Adverse Events Summary (**Table 4)**.

Potential Adverse Events

The following adverse events are among those that may occur in association with intra-articular injections:

- Arthralgia
- Joint stiffness
- Joint effusion
- Joint swelling
- Joint warmth
- Injection site pain
- Arthritis
- Arthropathy
- Gait disturbance

According to post-marketing experience of other sodium hyaluronate preparations, anaphylactic / anaphylactoid reactions accompanied by transient hypotension (sudden drop in blood pressure), have been rarely reported worldwide, all of which resolved either spontaneously or after conservative treatment.

Pivotal Clinical Trial

Study Design: The safety and efficacy of Gel-Syn was assessed in a prospective, randomized, double-blind, active control (commercial hyaluronan), non-inferiority study conducted at 23 centers in Europe (Czech Republic, France, Italy, Switzerland, Slovakia, and Germany). A total of 380 patients were enrolled. Patients were given 2 mL intra-articular injections of the randomly assigned Gel-Syn or commercial hyaluronan once a week for three consecutive weeks, with follow-up visits scheduled for weeks 4, 12 and 26. The primary efficacy variable for this study was the Western Ontario McMaster Universities (WOMAC) pain subscore at week 26 which was required to meet a delta of 8 mm, with secondary efficacy variables including WOMAC total score and stiffness and function subscores, Lequesne Algofunctional Index, global pain assessed by patient, global status assessed by patient and Investigator, paracetamol consumption, patient satisfaction, and overall clinical response based on OMERACT-OARSI criteria. Safety variables included adverse events, pain and local tolerability at the injection site, and global tolerability as assessed by both patient and Investigator.

Patient Population: The average age of the 380 intent-to-treat (ITT) patients, defined as receiving at least one intra-articular injection, was 65.0 years, the majority were female (72.9%), BMI ranged from 19.8 to 34.7 kg/m^2, and the mean duration of osteoarthritis in the target knee was 7.61 years. For 52.6% of the patients, the right knee was the target knee, but 66.1% also had osteoarthritis in the contralateral knee. The anatomical location of target knee osteoarthritis was usually in the medial tibio-femoral region (82.9%), with some degree of joint space narrowing being reported in nearly all patients (95.0%). Patient assessed global pain scores at the screening and baseline visits averaged 65.3 and 65.6, respectively, while the other indices of disease severity at these time-points (i.e. global status, range of motion, WOMAC & Lequesne scoring) were also suggestive of mild to moderate target knee osteoarthritis. The only baseline variable reaching statistical significance with regard to differences between the two treatment groups was venous insufficiency which was more prevalent for commercial hyaluronan patients (5.3% vs 1.0%, p =0.019), with hypercholesterolemia and the requirement for ambulatory assistance also being somewhat (but not statistically significantly) greater (11.7% vs 6.3%, p = 0.073 and 5.9% vs 2.1%, p = 0.069, respectively).

Efficacy Data: For the primary outcome measure (change from baseline), the protocol-defined 8 mm non-inferiority margin was met for all time points. In addition, the 95% lower-bound confidence interval of the difference (Gel-Syn minus commercial hyaluronan) in pain subscore reduction from baseline for the overall 26 week WOMAC pain subscore for the ITT patient population was -1.4 (see Change from Baseline – Overall, **Table 1**). Overall WOMAC pain subscore mean reduction from baseline was 30.8 mm(56%) for the Gel-Syn treatment group, in contrast to 29.4 mm (53%) for patients receiving commercial hyaluronan.

Table 1: Primary Endpoint (100 mm WOMAC Pain Subscore)* for Intent-To-Treat (ITT) Patients

	Gel-Syn		Commercial Hyaluronan			
Variable	N	Mean ± SE	N	Mean ± SE	Difference*	95% CI
Absolute Values						
Baseline	192	55.2 ± 0.8	188	55.5 ± 0.8	-0.3 ± 1.1	(-2.5, 1.9)
4 Weeks	189	27.0 ± 1.6	183	28.6 ± 1.7	-1.6 ± 1.7	(-4.9, 1.7)
12 Weeks	185	23.6 ± 1.6	178	25.6 ± 1.7	-2.0 ± 1.7	(-5.4, 1.4)
26 Weeks	181	22.2 ± 1.6	175	22.9 ± 1.7	-0.7 ± 1.7	(-4.1, 2.7)
Overall	.	24.3 ± 1.5	.	25.7 ± 1.6	-1.4 ± 1.5	(-4.3, 1.4)
Change from Baseline						
4 Weeks	189	28.1 ± 1.6	183	26.5 ± 1.7	1.6 ± 1.7	(-1.7, 4.9)
12 Weeks	185	31.5 ± 1.6	178	29.5 ± 1.7	2.0 ± 1.7	(-1.4, 5.4)
26 Weeks	181	32.9 ± 1.6	175	32.2 ± 1.7	0.7 ± 1.7	(-2.7, 4.1)
Overall	.	30.8 ± 1.5	.	29.4 ± 1.6	1.4 ± 1.5	(-1.4, 4.3)
* Gel-Syn minus Commercial Hyaluronan ± SE.						
Mixed models include factors for treatment, visit, treatment*visit interaction, center and baseline level.						

For the secondary study variables, because this was a non-inferiority study not designed to test superiority, no claims can be made about the statistical significance of any intergroup differences such as those observed at 26 weeks following either three Gel-Syn or commercial hyaluronan injections (**Table 2**).

Table 2: Secondary Outcome Variables for ITT Patients at 26 Weeks

	Gel-Syn (N=192)		Commercial Hyaluronan (N=188)		
Variable	N	Mean ± SE or %	N	Mean ± SE or %	p
1. WOMAC Function	181	28.3 ± 1.7	175	28.0 ± 1.8	0.860
2. WOMAC Stiffness	181	25.9 ± 1.8	175	25.2 ± 1.9	0.735
3. WOMAC Total Score	181	29.0 ± 1.6	175	28.6 ± 1.7	0.811
4. Lequesne Pain	181	2.08 ± 0.16	175	1.79 ± 0.17	0.097
5. Lequesne Walking	181	0.79 ± 0.10	175	0.66 ± 0.11	0.262
6. Lequesne Daily Living	181	1.23 ± 0.12	175	1.10 ± 0.13	0.320
7. Lequesne Total Score	181	4.07 ± 0.32	175	3.53 ± 0.33	0.124
8. Patient Global Pain	181	37.2 ± 2.2	175	33.6 ± 2.3	0.138
9. Patient Global Status	180	25.4 ± 2.0	175	25.7 ± 2.1	0.892
10. Paracetamol Usage	187	46.8 ± 9.7	183	62.8 ± 10.1	0.090
11. Patient Satisfaction	181	82.9%	174	77.0%	0.185
12. Investigator Global Status	181	85.0%	174	76.5%	0.043
13. OMERACT-OARSI	181	89.9%	175	87.7%	0.504
1 to 9: 26-Week Change from Baseline Score (higher=better). Mixed models include factors for treatment, visit, treatment*visit interaction, center and baseline level.					
10: Number of paracetamol rescue medication tablets over the entire 26 Weeks. Mixed model includes factors for treatment and center.					
11: Patients satisfied or very satisfied at 26 Weeks. Generalized Estimating Equation (GEE) logistic regression model includes factors for treatment, visit, treatment*visit interaction and center.					
12: Status good or very good at 26 Weeks. Generalized Estimating Equation (GEE) logistic regression model includes factors for treatment, visit, treatment*visit interaction, center and baseline level.					
13: OMERACT-OARSI Success at 26 Weeks. Generalized Estimating Equation (GEE) logistic regression model includes factors for treatment, visit, treatment*visit interaction and center.					

Safety Data**:**

Adverse Events – Of the 380 patients in the intent-to-treat (ITT) patient population, one or more adverse events were recorded for 160 (42.1%) sometime over the course of the study following the first injection of the assigned hyaluronic acid preparation, by far the most common being back pain (11.8%), arthralgia (10.5%), nasopharyngitis (8.9%), and headache (8.2%). Back pain, arthralgia, and headache were more common in the commercial hyaluronan treatment group than in the Gel-Syn treatment group (**Table 3**). Adverse events judged to be related to treatment, severe and/or serious were relatively rare (1.6%), and none of the serious adverse events were thought to be treatment-related (**Table 4**). Overall adverse event rates for the Gel-Syn treatment group were comparable to those of the commercial hyaluronan treatment group.

Table 3: ITT Patients – Adverse Events*

		Gel-Syn (N=192)			Commercial Hyaluronan (N=188)		
Variable	n†	n	Percent	n	n	Percent	p Values‡
Any Adverse Event	222	83	43.2%	220	77	41.0%	0.679
Gastrointestinal Disorders							
Toothache	8	7	3.6%	3	3	1.6%	0.337
Diarrhea	1	1	0.5%	4	3	1.6%	0.368
Abdominal pain upper	0	0	0.0%	2	2	1.1%	0.244
General Disorders/Administrative Site Conditions							
Pyrexia	6	5	2.6%	7	5	2.7%	1.000
Injection site pain	3	1	0.5%	4	3	1.6%	0.368
Hepatobiliary disorders							
Cholecystitis acute	0	0	0.0%	2	2	1.1%	0.244
Infections and infestations							
Nasopharyngitis	27	19	9.9%	22	15	8.0%	0.591
Respiratory tract infection	4	4	2.1%	3	3	1.6%	1.000
Urinary tract infection	4	4	2.1%	3	3	1.6%	1.000
Influenza	6	3	1.6%	3	3	1.6%	1.000
Cystitis	1	1	0.5%	5	4	2.1%	0.211
Herpes zoster	0	0	0.0%	2	2	1.1%	0.244
Viral infection	1	1	0.5%	2	2	1.1%	0.620
Musculoskeletal/Connective Tissue Disorders							
Back pain	25	19	9.9%	39	26	13.8%	0.268
Arthralgia	29	18	9.4%	28	22	11.7%	0.506
Pain in extremity	9	9	4.7%	4	2	1.1%	0.062
Musculoskeletal pain	6	5	2.6%	2	2	1.1%	0.449
Neck pain	3	1	0.5%	5	4	2.1%	0.211
Joint swelling	2	2	1.0%	5	2	1.1%	1.000
Nervous System Disorders							
Headache	29	13	6.8%	31	18	9.6%	0.353
Respiratory/Thoracic/Mediastinal Disorders							
Oropharyngeal pain	3	3	1.6%	2	2	1.1%	1.000

* Adverse events are included in this table only if the incidence in one of the treatment groups exceeded 1%.
† First n is number of events, and second n is number of patients experiencing an event.
‡ Fisher's exact test.

Table 4: ITT Patients – Adverse Events Based on Relationship to Treatment, Severity, Seriousness

	Gel-Syn (N=192)			Commercial Hyaluronan (N=188)			
Variable	n*	n	Percent	n	n	Percent	p Values†
Adverse Events Certainly, Probably Related to Treatment							
Any Adverse Event	1	1	0.5%	5	4	2.1%	0.211
General disorders and administration site conditions							
Injection site hematoma	0	0	0.0%	1	1	0.5%	0.495
Injection site pain	1	1	0.5%	1	1	0.5%	1.000
Musculoskeletal and connective tissue disorders							
Arthralgia	0	0	0.0%	1	1	0.5%	0.495
Joint swelling	0	0	0.0%	2	1	0.5%	0.495
Severe Adverse Events							
Any Adverse Event	1	1	0.5%	6	6	3.2%	0.065
Gastrointestinal Disorders							
Diverticulum intestinal	0	0	0.0%	1	1	0.5%	0.495
Hepatobiliary disorders							
Cholecystitis acute	0	0	0.0%	1	1	0.5%	0.495
Infections and infestations							
Influenza	0	0	0.0%	1	1	0.5%	0.495
Injury, poisoning and procedural complications							
Radius fracture	0	0	0.0%	1	1	0.5%	0.495
Musculoskeletal and connective tissue disorders							
Arthritis	0	0	0.0%	1	1	0.5%	0.495
Intervertebral disc protrusion	1	1	0.5%	0	0	0.0%	1.000
Surgical and medical procedures							
Hip arthroplasty	0	0	0.0%	1	1	0.5%	0.495
Serious Adverse Events							
Any Adverse Event	2	2	1.0%	5	4	2.1%	0.445
Gastrointestinal disorders							
Abdominal wall hematoma	1	1	0.5%	0	0	0.0%	1.000
Diverticulum intestinal	0	0	0.0%	1	1	0.5%	0.495
General disorders and administration site conditions							
Pyrexia	0	0	0.0%	1	1	0.5%	0.495
Hepatobiliary disorders							
Cholecystitis acute	0	0	0.0%	1	1	0.5%	0.495
Musculoskeletal and connective tissue disorders							
Arthritis	0	0	0.0%	1	1	0.5%	0.495
Intervertebral disc protrusion	1	1	0.5%	0	0	0.0%	1.000
Surgical and medical procedures							
Hip arthroplasty	0	0	0.0%	1	1	0.5%	0.495

* First n is number of events, and second n is number of patients experiencing an event.
† Fisher's exact test.

Pain at Injection Site/Local Tolerability – Pain associated with the initial injection of the experimental product or comparator in ITT patients averaged 2.95 on a 10 point scale, declining slightly to 2.80 then 2.65 after the second and third injections, respectively, with local tolerability being judged as good/very good by 91% to 93% of the patients at each of the visits following product administration.

Patient/Investigator Global Tolerability – Patient and investigator assessed global tolerability at the 4, 12 and 26-week follow-up visits were nearly identical and comparable to local tolerability scoring, as good/very good scores were obtained from 93% to 97% of the respondents. There were no statistically significant intergroup differences for any of these variables.

Post-Marketing Experience
Ten adverse events have been reported since Gel-Syn was first commercialized in Western Europe in 2002, including knee cooling, metallic taste, skin eruption, inflammatory symptoms, burning and itching sensations, tiredness, fever, psoitis, giant urticaria and edema in both legs, and gouty arthritis. In all the cases, the patients recovered without sequelae.

DETAILED DEVICE DESCRIPTION
Gel-Syn consists of a buffered physiological solution of 0.84% sodium hyaluronate (**Table 5**).

Table 5: Gel-Syn Components (per syringe)

Component Name	Unitary Amount
Sodium Hyaluronate	16.8 mg
Sodium Chloride	17.0 mg
Sodium Phosphate Dibasic Anhydrous	0.32 mg
Sodium Phosphate Monobasic Dehydrate	0.090 mg
Water for Injection	q.s to 2 mL

INTERACTIONS
None currently known.

HOW SUPPLIED
Gel-Syn is supplied as a sterile solution in a pre-filled glass syringe. One or three syringe(s) in individually sealed blisters are contained within a carton box.

SHELF LIFE
36 months.

STORAGE INSTRUCTIONS
- Gel-Syn should be stored at 20° to 25°C (68° - 77°F). DO NOT FREEZE.

DIRECTIONS FOR USAGE
1. Using an 18- to 22-guage needle, remove synovial fluid or effusion before injecting Gel-Syn.
2. To ensure a tight seal and prevent leakage during administration, secure the needle tightly while firmly holding the luer hub.
3. Inject the full 2 mL in one knee only.
4. Each Gel-Syn syringe is manufactured using aseptic filling technique. Therefore, do not use if the packaging is opened or damaged.
5. Use the product immediately once opened.

DISTRIBUTED BY: _____

MANUFACTURED BY:
IBSA Farmaceutici Italia
Via Martiri di Cefalonia 2
26900 Lodi
Italy

MANUFACTURED FOR:
Institut Biochimique SA (IBSA)
CH-6915 Pambio-Noranco, Switzerland