Package Insert

Gel-One®

Cross-linked Hyaluronate

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

DESCRIPTION

Gel-One® is a sterile, transparent, and viscoelastic hydrogel composed of cross-linked hyaluronate, a derivative of highly purified sodium hyaluronate (hyaluronan) extracted from chicken combs. Hyaluronan is a polysaccharide containing repeating disaccharide units of glucuronic acid and N-acetylglucosamine. In Gel-One®, strands of hyaluronan are bound to each other via dimers of cinnamic acid resulting in increased viscoelasticity.

INDICATIONS FOR USE

Gel-One® is indicated for the treatment of pain in osteoarthritis (OA) of the knee in patients who have failed to respond adequately to non-pharmacologic therapy, nonsteroidal anti-inflammatory drugs (NSAIDs), or simple analgesics, e.g., acetaminophen.

CONTRAINDICATIONS

- Do not administer Gel-One® to patients with known hypersensitivity (allergy) to Gel-One® or sodium hyaluronate preparations.
- Do not inject Gel-One® in the knees of patients having 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.
- Do not inject Gel-One® intravascularly.

PRECAUTIONS

General

- Strict aseptic administration technique must be followed.
- Remove joint effusion, if present, before injecting Gel-One®.
- The safety and effectiveness of the use of Gel-One® in joints other than the knee and for conditions other than OA have not been established.
- The safety and effectiveness of the use of Gel-One® concomitantly with other intra-articular injectables have not been established.
- The effectiveness of repeat treatment cycles of Gel-One® has not been established.

- Use caution when injecting Gel-One® into patients who are allergic to cinnamons, avian proteins, feathers, and/or egg products.
- The safety and effectiveness of Gel-One® in severely inflamed knee joints have not been established.
- Do not inject Gel-One® extra-articularly or into the synovial tissue and capsule.
- STERILE CONTENTS. The pre-filled syringe is intended for single use. The contents of the syringe must be used immediately after the packaging is opened. Discard any unused Gel-One®.
- Do not use Gel-One® if the blister package has been opened or damaged, or if there are cracks or breakage in the pre-filled syringe. Store in the original package below 77ºF (25ºC). DO NOT FREEZE. Do not use after expiration date indicated on package.

Patient Information

- Provide patients with a copy of the Patient Information prior to use.
- Transient pain, swelling, and/or effusion of the treated knee joint may occur after intra-articular injection of Gel-One®. These events are usually resolved on their own or with conservative treatment.
- As with any invasive joint procedure, it is recommended that the patient avoid any strenuous activities (such as jogging, tennis, other active sports, heavy lifting) and prolonged weight-bearing activities (such as standing for more than one hour) within 48 hours following the intra-articular injection of Gel-One®.

Use In Specific Populations

- **Pregnancy:** The safety and effectiveness of Gel-One® have not been established in pregnant women.
- **Nursing Mothers:** It is not known if Gel-One® is excreted in human milk. The safety and effectiveness of Gel-One® have not been established in lactating women.
- **Pediatrics:** The safety and effectiveness of Gel-One® have not been demonstrated in pediatric patients (≤ 21 years of age).

ADVERSE EVENTS

Reported Device-Related Adverse Events

The most common adverse events related to Gel-One® injection reported in the clinical studies were the following:

- Joint swelling
- Joint effusion
- Arthralgia

All adverse events related to Gel-One® injection reported in the clinical studies are provided in the Adverse Events Summary.

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.

CLINICAL STUDIES

13-Week Multicenter Safety and Effectiveness Study with 13-Week Open-Label Extension/Retreatment Safety Study

The safety and effectiveness of a single injection of Gel-One® for the treatment of symptomatic OA of the knee were studied in a prospective, randomized and double-blind controlled study conducted at 25 centers in the United States. The safety and effectiveness of a single injection of Gel-One® was confirmed by protocol SI-6606/01.

A total of 379 patients were randomized at a 2:1 ratio of Gel-One® (n=251) to phosphate buffered saline (PBS; n=128); both investigators and patients were blinded to treatment allocation. Data collection included patient-reported Western Ontario and McMaster Universities Osteoarthritis (WOMAC) visual analog scale (VAS) scores, Outcome Measures in Rheumatology Clinical Trials and Osteoarthritis Research Society International responses (OMERACT-OARSI responses), physician and patient global assessments and adverse events (AEs). The primary effectiveness analysis was a comparison, at 13 weeks, between Gel-One® and PBS treatment groups of change from baseline in WOMAC VAS Pain subscore, measured on a 100 mm scale.

The safety of a repeat injection of Gel-One® was studied in a multicenter, open-label, extension and retreatment study (Gel/1132) conducted at 23 centers in the United States following protocol SI-6606/01. Patients who had completed the 13-week blinded initial treatment pivotal study SI 6606/01 were eligible to enter the Gel/1132 extension study for prolonged follow-up and possible retreatment.

Patient Population and Demographics

Of the 379 enrolled patients, 377 patients received either Gel-One® or PBS injection, and 375 patients were analyzed for the Intent to treat (ITT) population. Patients reported pain with symptomatic OA of the knee defined by WOMAC VAS Pain subscore of ≥40 mm in the study knee and ≤20 mm in the contralateral knee. Patients meeting the following criteria were excluded at randomization; Kellgren-Lawrence (K-L) Grade 4, severe inflammation or joint effusion in either knee. The ITT population included all treated patients who had any post-injection evaluations. Table 1 summarizes baseline and patient demographic characteristics for the ITT population. A total of 125 patients were retreated with Gel-One® after receiving a Gel-One® injection in the initial trial.

Table 1. Patient Baseline Characteristics – ITT Population, Study SI-6606/01

Variable		**Gel-One® (N=247)**	**PBS (N=128)**
Age (years)	Mean (SD)	60.9 (10.2)	60.3 (10.0)
Gender (n)	Male	100 (40.5%)	51 (39.8%)
	Female	147 (59.5%)	77 (60.2%)
K-L Score – Study Knee (n)	1	21 (8.5%)	18 (14.1%)
	2	94 (38.1%)	47 (36.7%)
	3	132 (53.4%)	63 (49.2%)
Study Knee			
WOMAC Pain Subscore (mm)	Mean (SD)	70.7 (14.4)	68.0 (13.1)
Total WOMAC Score (mm)	Mean (SD)	69.5 (16.0)	67.8 (14.7)
WOMAC Physical Function (mm)	Mean (SD)	68.9 (17.4)	67.6 (15.8)
WOMAC Stiffness (mm)	Mean (SD)	71.6 (17.5)	69.3 (17.3)
Contralateral Knee			
WOMAC Pain Subscore (mm)	Mean (SD)	7.3 (5.5)	7.6 (5.6)

There were no significant demographic or baseline differences between patients who did and did not receive retreatment with Gel-One® in the Gel/1132 open-label study. There were also no significant demographic or baseline differences between patients who did and did not enroll in the Gel/1132 open-label study.

Treatment and Evaluation Schedule

Following an initial screening visit, eligible patients were randomized to receive either a single injection of Gel-One® or a single injection of PBS. Patients in both treatment groups received an intra-articular injection in the identified knee joint at Week 0. Effectiveness and safety measures were assessed by follow-up visits at Weeks 1, 3, 6, 9, and 13.

Patients, who used NSAIDs at stable doses over 4 weeks prior to study injection, were allowed to continue with the same regimen. Intermittent use of short-acting opiates was allowed during the

study. Acetaminophen was provided to patients as a rescue medication up to 4,000 mg per day. All medication was prohibited within 24 hours prior to each evaluation visit.

Patients who entered the extension study were evaluated at screening (Week 0), and then at Weeks 3, 6, 9, and 13 of the extension phase. Patients could receive retreatment with a single injection of Gel-One® in the treatment knee if and when their response to the original injection worsened to the extent that they met the original study pain eligibility criteria. Patients who qualified for retreatment during this 13-week period were then followed for 13 weeks (at Weeks 1, 3, 6, 9, and 13 after retreatment). Patients who did not qualify during this 13-week period exited the extension study without receiving retreatment.

Adverse Events Summary

Among the Gel-One® treatment group (249 patients), 483 adverse events in 172 patients (69.1%) were reported. Among the PBS treatment group (128 patients), 216 adverse events in 81 patients (63.3%) were reported. There was no statistically significant difference in the incidence rates of adverse events between Gel-One® and PBS treatment groups. Adverse events occurring in more than 5% of patients in both treatment groups included joint swelling (knee), joint effusion (knee), arthralgia (knee or hip) and upper respiratory tract infections (Refer to Table 2).

In the Gel-One® retreatment group (125 patients), 76 adverse events in 50 patients (40.0%) were reported in the 4 weeks following the second Gel-One® treatment. There was no statistically significant difference in the incidence rates of adverse events between the Gel-One® retreatment and PBS groups. Adverse events occurring in more than 5% of patients in both treatment groups included joint effusion, arthralgia, and joint swelling (Refer to Table 2).

Table 2. Adverse Events Occurring in ≥ 5% of Treated Patients

System Organ Class	Preferred Term	Gel-One® (N=249)	PBS (N=128)	Retreatment (N=125)
Musculoskeletal and connective tissue disorders	Joint swelling (knee)	70 (28.1%)	36 (28.1%)	10 (8.0%)
	Joint effusion (knee)	58 (23.3%)	33 (25.8%)	13 (10.4%)
	Arthralgia (knee/hip)	44 (17.7%)	15 (11.7%)	12 (9.6%)
Infections and infestations	Upper respiratory tract infections	16 (6.4%)	6 (4.7%)	0

The most common adverse events related to Gel-One® injection reported in study SI-6606/01 were joint swelling (14.1%), joint effusion (11.2%), and arthralgia (7.6%).

Additional adverse events related to Gel-One® injection included injection site pain (2.0%), joint stiffness (0.8%), muscular weakness (0.8%), dizziness (0.8%), erythema (0.8%), effusion (0.4%), injection site bruising (0.4%), injection site erythema (0.4%), swelling (0.4%), increased alanine aminotransferase (0.4%), increased white blood cell count (0.4%), back pain (0.4%), muscle spasms (0.4%), synovitis (0.4%), tension headache (0.4%), rash (0.4%), rash pruritic (0.4%) and hypertension (0.4%) (Refer to Table 3).

The most common adverse events related to Gel-One® repeat injection were arthralgia (7.2%), joint swelling (5.6%), joint effusion (4.8%), and injection site pain (2.4%).

Additional adverse events related to Gel-One® repeat injection included injection site bruising (0.8%), injection site reaction (0.8%), and migraine (0.8%).

There were neither serious adverse events nor pseudoseptic reactions related to the initial or repeat Gel-One® injections.

Table 3. Adverse Events Related to Study Treatment

System Organ Class	Preferred Term	Gel-One® (N=249)	PBS (N=128)	Retreatment (N=125)
Musculoskeletal and connective tissue disorders	Joint swelling (knee)	35 (14.1%)	15 (11.7%)	7 (5.6%)
	Joint effusion (knee)	28 (11.2%)	13 (10.2%)	6 (4.8%)
	Arthralgia (knee/hip)	19 (7.6%)	12 (9.4%)	9 (7.2%)
	Joint stiffness (knee)	2 (0.8%)	1 (0.8%)	0
	Muscular weakness (knee)	2 (0.8%)	1 (0.8%)	0
	Back pain	1 (0.4%)	1 (0.8%)	0
	Joint warmth (knee)	0	1 (0.8%)	0
	Muscle spasms (knee)	1 (0.4%)	0	0
	Synovitis (knee)	1 (0.4%)	0	0
General disorders and administration site conditions	Injection site pain	5 (2.0%)	1 (0.8%)	3 (2.4%)
	Effusion	1 (0.4%)	1 (0.8%)	0
	Injection site erythema	1 (0.4%)	1 (0.8%)	0
	Injection site bruising	1 (0.4%)	0	1 (0.8%)
	Injection site reaction	0	0	1 (0.8%)
	Swelling	1 (0.4%)	0	0
Skin and subcutaneous tissue disorders	Erythema	2 (0.8%)	0	0
	Rash	1 (0.4%)	0	0
	Rash pruritic	1 (0.4%)	0	0
Nervous system disorders	Headache	0	2 (1.6%)	0
	Dizziness	2 (0.8%)	0	0
	Burning sensation	0	1 (0.8%)	0
	Tension headache	1 (0.4%)	0	0
	Migraine	0	0	1 (0.8%)
Investigations	Increased alanine aminotransferase	1 (0.4%)	0	0
	Increased white blood cell count	1 (0.4%)	0	0
Vascular disorders	Hypertension	1 (0.4%)	0	0
Ear and labyrinth disorders	Hearing impaired	0	1 (0.8%)	0
Infections and infestations	Cellulitis	0	1 (0.8%)	0
Injury, poisoning and procedural complications	Contusion	0	1 (0.8%)	0

Clinical Effectiveness Results

The study primary endpoint, WOMAC Pain subscore at Week 13, demonstrated that Gel-One® was superior to PBS with a 6.39 mm advantage at Week 13 in the ITT population of the SI 6606/01 study (p = 0.0374) (Refer to Table 4 and Figure 1).

Summary of secondary effectiveness results are shown in Tables 5 and 6.

Figure 1. Improvement from Baseline in WOMAC VAS Pain Subscore at Week 13 – ITT Population, Study SI-6606/01

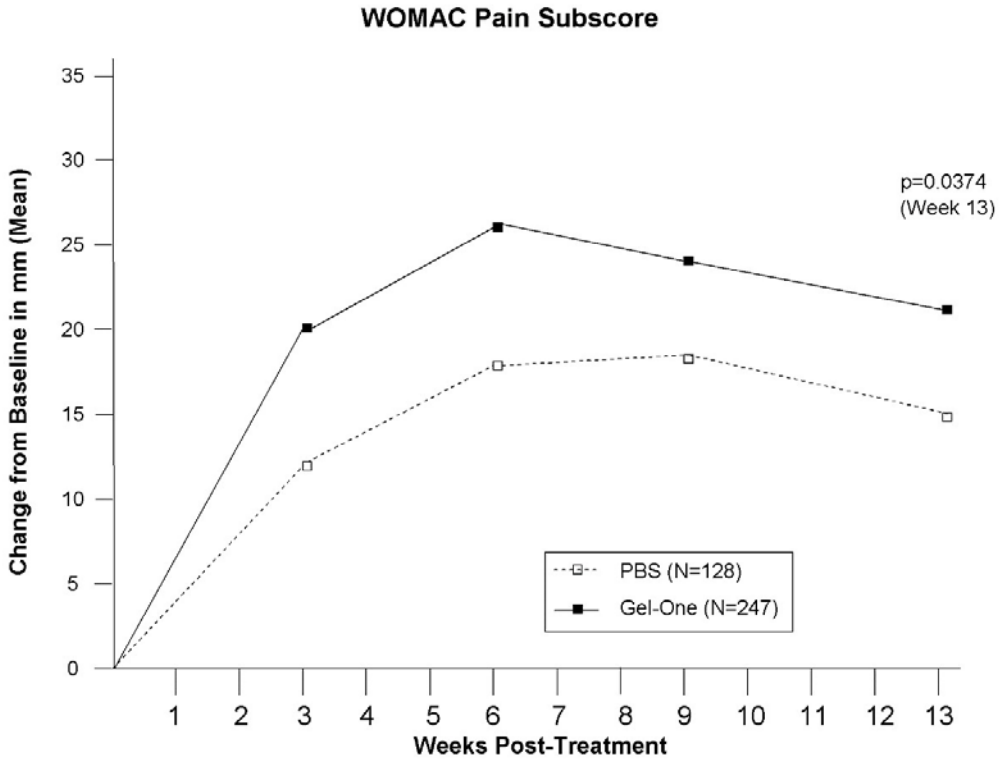

Table 4. WOMAC[a] VAS Pain Improvement from Baseline at 13 weeks – ITT Population, Study SI-6606/01 (N=375)[b]

Assessed Time-point	Model-Estimated Advantage (Gel-One® - PBS)	Two- sided Lower 95% Confidence Limit (mm)	Two-sided P-value
At Week 13	6.39 mm	0.37	0.0374

[a] The WOMAC Index is a set of standardized questionnaires used by health professionals to evaluate the condition of patients with OA of the knee and hip. WOMAC Pain Scale is 100 mm.

[b] The analysis is based on the quadratic spline model at knot of 6 weeks and at week 13 for the primary endpoint.

Table 5. OMERACT-OARSI Responses[a] – ITT Population, Study SI-6606/01

Odds Ratio[b]	Two-sided Lower 95% Confidence Limit of Odds Ratio[c]	Two-sided P-valued
1.27	0.85	0.2418

[a] A subject was considered an OMERACT-OARSI 'responder' if either of the following 2 criteria were met:

(1) his or her reported improvement from baseline in WOMAC VAS Pain subscore or WOMAC VAS Physical Function subscore was at least 50% and the absolute change was at least 20 mm, or

(2) his or her reported improvement from baseline was at least 20% and the absolute change was at least 10 mm for at least 2 of the following 3 measures:

(a) WOMACVAS Pain subscore,

(b) WOMAC VAS Physical Function subscore,

(c) Subject Global Evaluation.

[b] $e^{(\text{Log Odds Ratio})} = 1.27$, based on GEE model
(Log Odds Ratio) = $\log_e$ [probability(responder)/ probability (non-responder)]Gel-One / [probability
(responder)/ probability(non-responder)]PBS

[c] When odds ratio >1, [probability(responder)/ probability (non-responder)Gel-One] > [probability (responder)/ probability (non- responder) PBS] and thus in favor of Gel-One.

[d] Statistically not significant

Table 6. Summary of Secondary Effectiveness[a] Endpoints at Week 13 – ITT Population, Study SI-6606/01

Effectiveness Measures[b]	Model-Estimated Advantage (Gel-One® - PBS)	Two-sided Lower 95% Confidence Limit (mm)	Two-sided P-value[c]
Total WOMAC Score	5.64 mm	-0.20	0.0583
WOMAC Stiffness	4.91 mm	-1.31	0.1216
WOMAC Physical Function	5.42 mm	-0.47	0.0714

[a] Based on the quadratic spline model at week 13.
[b] WOMAC Scale is 100 mm.
[c] P-value was not adjusted for multiplicity of secondary endpoints.

26-Week Multicenter Safety and Effectiveness Study

The safety and effectiveness of a single injection of Gel-One® for the treatment of symptomatic OA of the knee were studied in Gel/1133, a multicenter, randomized, double-blind, PBS-controlled study conducted at 38 centers in the United States.

Patient Population and Demographics

Of the 814 treated patients, 404 patients were injected with Gel-One®, and 410 patients were injected with PBS. Patients reported pain with symptomatic OA of the knee defined by a pain score of 50 mm to 90 mm (inclusive) in the study knee and <30 mm in the contralateral knee, recorded on a 100-mm VAS immediately following a 50-foot walk. Patients with a K-L score of Grade 4, or severe joint inflammation or effusion in the target knee were excluded. The ITT population included all treated patients who had at least 1 post-injection visit. Table 7 summarizes baseline and patient demographic characteristics for the ITT population. There were no significant demographic or baseline differences between patients who did and did not receive retreatment with Gel-One® in the Gel/1133 study.

Table 7. Patient Baseline Characteristics – ITT Population, Gel/1133

Variable		**Gel-One® (N=402)**	**PBS (N=407)**
Age (years)	Mean (SD)	59.3 (9.1)	59.8 (9.3)
Gender (n)	Male	181 (45.0%)	173 (42.5%)
	Female	221 (55.0%)	234 (57.5%)
K-L Score – Study Knee (n)	1	113 (28.1%)	111 (27.3%)
	2	161 (40.0%)	164 (40.3%)
	3	128 (31.8%)	132 (32.4%)
50-foot Walk VAS Pain Score (mm)			
Study Knee	Mean (SD)	69.25(7.64)	69.36 (7.82)
Contralateral Knee	Mean (SD)	11.50 (7.54)	11.95 (7.57)

Treatment and Evaluation Schedule

Following an initial screening visit, eligible patients were randomized to receive either a single injection of Gel-One® or a single injection of PBS. Patients in both treatment groups received an intra-articular injection in the identified knee joint at Week 0. Effectiveness and safety measures were assessed by follow-up visits at Weeks 3, 6, 12, 18, and 26.

Certain concomitant medications were prohibited, including opioids and most corticosteroids. Acetaminophen was provided to patients as a rescue medication up to 1,000 mg per day. All medication to treat OA knee pain was prohibited within 24 hours prior to each evaluation visit.

Adverse Events Summary

Among the Gel-One® treatment group (404 patients), 421 adverse events were reported in 185 (45.8%) patients. Among the PBS treatment group (410 patients), 421 adverse events were reported in 197 (48.0%) patients. There was no statistically significant difference in the incidence rates of adverse events between Gel-One® and PBS treatment groups. Adverse events occurring in more than 5% of patients in both treatment groups included arthralgia, joint swelling, and joint effusion (Refer to Table 8).

Table 8. Adverse Events Occurring in > 5% of Treated Patients

System Organ Class	Preferred Term	Gel-One® (N=404)	PBS (N=410)
Musculoskeletal and connective tissue disorders	Arthralgia	44 (10.9%)	42 (10.2%)
	Joint swelling	33 (8.2%)	42 (10.2%)
	Joint effusion	30 (7.4%)	29 (7.1%)

The most common adverse events related to Gel-One® injection reported in Study Gel/1133 were arthralgia (3.2%), joint swelling (1.7%), and joint effusion (1.0%).

Additional adverse events related to Gel-One® injection included joint crepitation (0.2%), joint stiffness (0.2%), injection site joint pain (1.0%), injection site joint swelling (0.5%), injection site joint effusion (0.2%), oedema peripheral (0.2%), and urticaria (0.2%) (Refer to Table 9).

There were no serious adverse events related to the Gel-One® injections.

Table 9. Adverse Events Related to Study Treatment

System organ class	Preferred Term	Gel-One® (N=404)	PBS (N=410)
Musculoskeletal and connective tissue disorders	Arthralgia	13 (3.2%)	10 (2.4%)
	Joint swelling	7 (1.7%)	6 (1.5%)
	Joint effusion	4 (1.0%)	4 (1.0%)
	Joint crepitation	1 (0.2%)	0
	Joint stiffness	1 (0.2%)	2 (0.5%)
	Arthropathy	0	1 (0.2%)
	Joint range of motion decreased	0	1 (0.2%)
	Osteoarthritis	0	1 (0.2%)
General disorders and administration site conditions	Injection site joint pain	4 (1.0%)	6 (1.5%)
	Injection site joint swelling	2 (0.5%)	0
	Injection site joint effusion	1 (0.2%)	1 (0.2%)
	Oedema peripheral	1 (0.2%)	0
	Injection site joint redness	0	1 (0.2%)

	Injection site pruritus	0	1 (0.2%)
Skin and subcutaneous tissue disorders	Urticaria	1 (0.2%)	0
	Erythema	0	1 (0.2%)
	Pruritus generalised	0	1 (0.2%)
Nervous system disorders	Presyncope	0	1 (0.2%)

Clinical Effectiveness Results

26-Week Multicenter Safety and Effectiveness Study

In the Gel/1133 study, Gel-One® did not demonstrate superiority over PBS for the primary effectiveness endpoint of reduction in pain as measured by the 50-foot walk test over a 26-week evaluation period (p = 0.988). The Gel-One® treatment group did show more than a 40% improvement in 50-foot walk test pain score over baseline at all follow- up time points, which was clinically important, but, as shown below in Table 10, there was no statistically significant difference between the results in the Gel-One® and PBS treatment groups.

Table 10. Mean Improvement in VAS Pain Subscore (Following 50-Foot Walk Test) from Baseline at 26 Weeks 50-Foot Walk Test – ITT Population, Gel/1133 Study (N=809)

	PBS (N = 407)		Gel-One® (N = 402)			P-value
	Actual	Change from Baseline	Actual	Change from Baseline	Difference 95% CI	
Baseline	69.36 (SD=7.82)		69.25 (SD=7.64)			0.988
LS mean		-31.7		-31.7	0.0 (-2.7, 2.7)	

Post Hoc Non-Inferiority Analysis

A post-hoc non-inferiority analysis was performed to examine the effectiveness of a single injection of Gel-One® relative to three injections of Euflexxa, previously approved under P010029/S008. The Euflexxa FLEXX trial[1] shared many protocol design elements with the Gel-One® protocol (Gel/1133), primarily that the key effectiveness outcome was the pain scores measured following a 50-foot walk test on a 100-mm VAS pain scale and the study follow-up time period was 26 weeks for both protocols for an identical indication for use. The non-inferiority test would assess whether the improvement experienced by the Gel-One® group on a 100-mm VAS scale showed a similar degree of pain relief degree to that reported for the Euflexxa group.

Comparison of Gel/1133 Study and FLEXX Trial

The primary effectiveness endpoint and study objective for the indication for use were identical in the Gel/1133 and FLEXX studies. While the dose regimen in each study differed, with three weekly injections for Euflexxa and a single injection for Gel-One®, the follow-up points after the

completion of treatment in the FLEXX trial matched those of the Gel/1133 study. The inclusion/exclusion criteria of the two studies were generally similar. The mean ages and distributions of female and male subjects were similar between the two studies. Subjects in the two studies were limited to only acetaminophen as an analgesic rescue medication during the study. These similarities in the two studies served to justify comparison of the two data sets under a non-inferiority analysis.

Data Analyzed

The mean and standard error were calculated for the change from baseline in the pain scores following a 50-foot walk test on the 100-mm VAS for all ITT subjects (n=402) treated with Gel-One® in the Gel/1133 study. The mean and standard error for the change from baseline in the pain scores following a 50-foot walk test on the 100-mm VAS for Euflexxa were obtained from the publication by Altman et al.[1] on the FLEXX trial and were based on the full ITT set (n=291) of subjects treated with Euflexxa in the this trial.

Non-Inferiority Analysis Methodology

The Gel/1133 and the FLEXX studies shared nearly identical analyses of their primary outcome. Both modeled the change from baseline in VAS pain scores following the 50-foot walk test in a repeated measures mixed model across time points including Weeks 3, 6, 12, 18, and 26 with fixed effects for visit, treatment, a visit-by-treatment interaction, and a baseline covariate; thus, the estimated change from baseline from the two models share a consistent interpretation. Under the assumption two samples are independent, the standard error of the difference between the two estimates was estimated as $\sqrt{}(SE1^2+SE2^2)$, where SE1 and SE2 are the standard errors of the two estimates.

A non-inferiority margin of 5 mm (on the 100-mm VAS pain scale) was chosen for this analysis based on publically available SSEDs for two recently approved viscosupplement devices, Monovisc (P090031) and Hymovis (P150010).

The analysis tested the null hypothesis that the change from baseline in the VAS pain scores following the 50-foot walk test at Week 26 in the Gel-One® arm in Gel/1133 (δ_{GelOne}) was within 5 mm (or better) than the reported change from baseline for the Euflexxa arm for the FLEXX trial ($\delta_{Euflexxa}$).

This null hypothesis can be expressed as the hypothesis test:

H0: $\delta_{GelOne} - \delta_{Euflexxa} > 5$ vs. HA: $\delta_{GelOne} - \delta_{Euflexxa} \leq 5$

Non-Inferiority Analysis Results

The results of this non-inferiority analysis of Gel-One® and Euflexxa are shown below in Table 11.

Table 11. Non-Inferiority Comparison of Mean Changes in VAS Pain Score (Following 50-Foot Walk Test) from Baseline at 26 Weeks between Gel-One® and Euflexxa

Outcome at 26 Weeks	Euflexxa	Gel-One®
Change from baseline (95% CI)	-25.7 (-29.0, -22.4)	-29.5 (-32.1, -26.9)
Difference (95% CI)*	-3.8 (-inf, -0.3)	

* Gel-One® estimate minus Euflexxa's estimate. Standard Error (SE) is estimated as $\sqrt{(SE1^2+SE2^2)}$, where SE1 and SE2 are the standard errors of the two estimates. 95% CI is a one-sided test for non-inferiority.

This post hoc non inferiority analysis demonstrated Gel-One® to be non-inferior to Euflexxa at 26 weeks in pain reduction scores. There was a measure of uncertainty to this analysis due to the fact that this analysis did not incorporate a direct comparison of the differences between the viscosupplement treatment groups and their respective placebo treatment groups.

DETAILED DEVICE DESCRIPTION

Each pre-filled syringe with 3 mL of Gel-One® contains:

Cross-linked Hyaluronate	30.0 mg
Sodium Chloride	24.3 mg
Dibasic Sodium Phosphate Dodecahydrate	0.89 mg
Sodium Dihydrogen Phosphate Dihydrate	1.93 mg
Water for Injection	q.s. to 3 mL

HOW SUPPLIED

Gel-One® is supplied in a 3-mL, disposable, pre-filled glass syringe containing 3 mL of Gel-One®. The content of the syringe is sterile. The product is latex-free.

STORAGE INSTRUCTIONS

Do not use Gel-One® if the blister package has been opened or damaged, or if there are cracks or breakage in the pre-filled syringe. Store in the original package below 77ºF (25ºC). DO NOT FREEZE. Do not use after expiration date indicated on package.

INSTRUCTIONS FOR USE

Precaution: STERILE CONTENTS. The pre-filled syringe is intended for single use. The contents of the syringe must be used immediately after the packaging is opened. Discard any unused Gel-One®.

Warning: Do not concomitantly use disinfectants containing quaternary ammonium salts for skin preparation because sodium hyaluronate can precipitate in their presence.

Gel-One® is delivered in a single-use, pre-filled disposable glass syringe. This pre-filled syringe is composed of a rubber piston [butyl rubber: latex free], rubber tip cap [butyl rubber: latex free],

finger grip and plunger rod and is packaged in a molded plastic A- PET film blister with a Tyvek® lid.

Gel-One® is designed to be a single intra-articular injection into the knee joint.

1. Strict aseptic administration technique must be followed.

2. Remove joint effusion, if present, through an 18-20 G needle before injecting Gel-One®. Maintain needle placement in the joint while disconnecting the syringe used to relieve joint effusion. Discard the syringe containing the removed joint effusion. The same syringe should not be used for both removing effusion and injecting Gel-One®.

3. Peel off the blister Tyvek® lid from the blister package and remove the syringe.

4. Carefully remove the tip cap of the syringe and aseptically attach the syringe to an 18-20 G needle. To ensure a tight seal and to prevent leakage during administration, secure the needle tightly while firmly holding the luer lock. If effusion was previously removed, connect the syringe to the needle already placed in the joint. Twist the tip cap before pulling it off to minimize product leakage.

5. Inject Gel-One® into the knee joint through the needle using aseptic injection technique.

6. Inject the full, 3.0 mL of Gel-One®, into knee. If treatment is being administered to both knees, use a separate syringe of Gel-One® for each knee.

7. Injection of subcutaneous lidocaine or similar local anesthetic may be performed prior to injection of Gel-One®.

8. Discard any unused Gel-One®.

REFERENCES

1. Altman RD, Rosen JE, Bloch DA, Hatoum HT, Korner P. A Double-Blind, Randomized, Saline-Controlled Study of the Efficacy and Safety of EUFLEXXA® for Treatment of Painful Osteoarthritis of the Knee, With an Open-Label Safety Extension (The FLEXX Trial). Semin Arthritis Rheum 2009. 39(1):1-9.