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, non-steroidal 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 osteoarthritis 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 safety and effectiveness of a repeat treatment cycle of Gel-One® have 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 study are the following:

- Joint swelling
- Joint effusion
- Arthralgia

All adverse events related to Gel-One® injection reported in the clinical study 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 STUDY

Study Design

The safety and effectiveness of a single injection of Gel-One® for the treatment of symptomatic osteoarthritis 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 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.

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 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.

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.

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).

The most common adverse events related to Gel-One® injection reported in this study 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).

There were neither serious adverse events nor pseudoseptic reactions related to Gel-One® injection.

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 (p=0.0374) (Refer to Table 4 and Figure 1).

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

DETAILED DEVICE DESCRIPTION

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

Cross-linked Hyaluronate	30.0mg
Sodium Chloride	24.3mg
Dibasic Sodium Phosphate Dodecahydrate	0.89mg
Sodium Dihydrogen Phosphate Dihydrate	1.93mg
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.

Table 1. Patient Baseline Characteristics – ITT Population

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)

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

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

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 hyaluronan 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®.

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Table 3. Adverse Events Related to Study Treatment

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

Figure 1. Improvement from Baseline in WOMAC VAS Pain Subscore at Week 13 – ITT Population

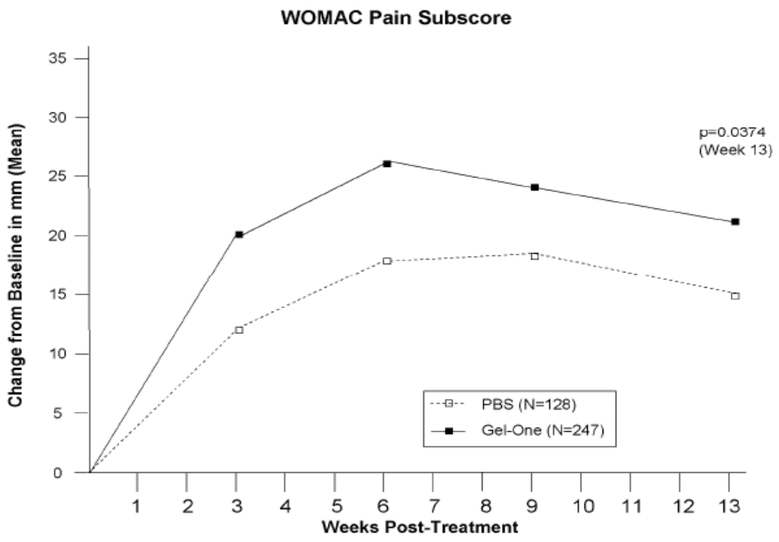

Table 4. WOMAC[a] VAS Pain Improvement from Baseline at 13 weeks (ITT Population (N=375))[b]

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 Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) is a set of standardized questionnaires used by health professionals to evaluate the condition of patients with osteoarthritis of the knee and hip. WOMAC Pain Scale is 100mm.

[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

Odds Ratio[b]	Two-sided Lower 95% Confidence Limit of Odds Ratio[c]	Two-sided P-value[d]
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)]$_{\text{Gel-One}}$ / [probability (responder)/ probability(non-responder)]$_{\text{PBS}}$

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

[d] Statistically not significant

Table 6. Summary of Secondary Effectiveness[a] Endpoints at Week 13 – ITT Population

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 100mm.

[c] P-value was not adjusted for multiplicity of secondary endpoints.

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