Patient Information

Gel-One®

Be sure to read the following important information carefully. This information does not take the place of your doctor’s advice. Your doctor has determined that the knee pain you are experiencing is caused by osteoarthritis and that you are a candidate for a non-surgical, non-pharmacological, pain-relieving therapy called Gel-One®. If you do not understand the following information or want to know more, ask your doctor.

Glossary of Terms

Hyaluronan: Hyaluronan is a natural substance found in the human body and is present in very high amounts in joints. The body's own hyaluronan acts like a lubricant and shock absorber in the joint and is needed for the joint to work properly.

Non-steroidal anti-inflammatory drug: Non-steroidal anti-inflammatory drugs are often abbreviated to “NSAIDs”. NSAIDs are drugs for reducing pain, fever and inflammation, such as aspirin and ibuprofen.

Osteoarthritis (OA): Osteoarthritis is a condition that involves the wearing down of cartilage (the protective covering on the ends of your bones) and loses cushioning fluid in the joint.

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What is Gel-One®?

Gel-One® is a transparent, sterile, and viscoelastic gel made from sodium hyaluronate (hyaluronan). Hyaluronan that is used to make Gel-One® comes from chicken combs and is highly purified. Hyaluronan is also a natural substance found in the human body and is present in very high amounts in joints. The body's own hyaluronan acts like a lubricant and shock absorber in the joint and is needed for the joint to work properly. Osteoarthritis (OA) is a condition that involves the wearing down of cartilage (the protective covering on the ends of your bones). In joints with OA, there may not be enough hyaluronan, and there may be lower quality of hyaluronan in joint fluid and tissues. Gel-One® is available in a 3.0 mL (approximately ½ teaspoon) pre-filled syringe. Gel-One® is injected directly into your knee joint.

What is Gel-One® used for?

Gel-One® is used to relieve knee pain due to OA. It is used for patients who do not get enough relief from non-steroidal anti-inflammatory drugs (NSAIDs) or from simple pain medications, such as acetaminophen, or from exercise and physical therapy.

Are there any reasons why I should not receive Gel-One®?

- You should not receive a Gel-One® injection if you have had any previous allergic reaction to Gel-One® or similar material, i.e., hyaluronan products. Signs of an allergic reaction may include swelling of your face, tongue, or throat; difficulty breathing or swallowing; shortness of breath; wheezing; chest pain; a tightness in your throat; sleepiness; rash; itching; hives; flushing; and/or fever.

- You should not have an injection into the knee if you have a skin disease or infections around the area where the injection will be given.

What should my doctor warn me about?

The following are important treatment considerations for you to discuss with your doctor and understand in order to help avoid unsatisfactory results and complications:

- Gel-One® is only for injection into the knee, performed by a qualified doctor.

- Gel-One® has not been tested to show better pain relief or safety when combined with other injected medicines.

- Tell your doctor if you are allergic to hyaluronan products.

- Tell your doctor if you are allergic to cinnamon or products from birds such as feathers, eggs, and poultry.
• For 48 hours after you receive the injection, you should avoid any strenuous activities (such as jogging, tennis, other active sports, heavy lifting) and prolonged weight-bearing activities such as standing on your feet for more than one hour.

• The safety and effectiveness of repeat treatment cycles of Gel-One® have not been established.

• Use of Gel-One® in joints other than the knee and for conditions other than OA has not been tested.

• Gel-One® has not been tested in pregnant or nursing women. You should tell your doctor if you think you are pregnant or if you are nursing a child.

• Gel-One® has not been tested in children (≤ 21 years of age).

What are the possible complications?

• Common side effects (also called reactions) are sometimes seen when Gel-One® is injected into the knee joint. These can include: knee pain, swelling, and/or fluid build-up around the knee. These reactions are generally mild and do not last long. Reactions are generally treated by resting and applying ice to the injected knee. Sometimes it is necessary to give pain relievers by mouth such as acetaminophen or NSAIDs, or to give injections of steroids, or to remove fluid from the knee joint. Patients rarely undergo arthroscopy (a surgical inspection of the knee joint) or other medical procedures related to these reaction.

• Other adverse events observed in the clinical study are shown in the section "What adverse events were observed in the clinical study?".

• Rare cases of allergic/non-allergic reaction to other hyaluronan preparations, accompanied by cold sweat, paleness and low blood pressure, have been reported.

• If any of these symptoms or signs appear after you are given Gel-One® or if you have any other problems, you should call your doctor.

What are the potential benefits of Gel-One®?

A clinical study involving 377 patients with knee pain due to OA was performed in the United States. The study investigated the safety and effectiveness of Gel-One®. Patients with osteoarthritic knee joint pain, who had not obtained pain relief with other medications, received either one injection of Gel-One® or saline control (salt water) into the knee joint. Pain of the knee joint was measured at various times over 13 weeks. The patients given Gel-One® had more pain relief than the patients given a saline injection for up to 13 weeks after injection.
How is Gel-One® given?

Your doctor will inject Gel-One® into your knee joint. Your doctor may recommend a local anesthetic to reduce the possible discomfort associated with an injection.

What do I need to do after I get Gel-One®?

For 48 hours after you receive the injection, you should avoid any strenuous activities (such as jogging, tennis, other active sports, heavy lifting) and prolonged weight-bearing activities (such as standing on your feet for more than one hour).

What other treatments are available for osteoarthritis?

If you have OA, there are several things you can do besides getting a Gel-One® injection. These include:

Non-drug treatments
- Avoiding activities that cause pain in your knee
- Exercise
- Physical therapy
- Weight loss
- Removal of excess fluid from the knee

Drug Therapy
- Pain medications such as acetaminophen and narcotics
- Drugs that reduce inflammation, such as aspirin, and other non-steroidal anti-inflammatory agents (NSAIDs) such as ibuprofen and naproxen (signs of inflammation are swelling, pain, or redness)
- Corticosteroids that are injected directly into the knee joint

When should I call my doctor?

If any of the side effects or symptoms described above appear after you are given Gel-One®, or if you have any other problems, you should call your doctor.

What did the clinical study show?

The study was conducted in the United States. A total of 377 patients received treatments, 249 patients were injected Gel-One® and 128 patients were injected saline control. Patients were asked to rate their pain during 5 conditions of activity or rest: how much pain during walking on a flat surface, during going up or down stairs, at night in bed, during sitting or lying down, and during standing. Patients rated their pain from 0 to 100 (bad pain) by marking on a 100 mm line. Pain was evaluated in this manner at 1, 3, 6, 9, and 13 weeks after injection. The pain scores were used to compare the effectiveness of Gel-One® injection to saline control injection. Patients receiving Gel-One® experienced
more improvement in knee pain over 13 weeks than patients who received saline control injections. The pain score was reduced by an average of 39.3% and average pain score reduction of 27.8 mm (on the 100mm pain scale) from the baseline score in patients receiving Gel-One®, whereas the pain score was reduced by an average of 33.2% with an average pain score reduction of 22.6 mm in patients receiving saline as a control.

**What adverse events were observed in the clinical study?**

The most common adverse events that were related to the Gel-One® injection were knee pain, swelling, and effusion. No device-related serious adverse events were observed in the clinical study.

Other adverse events were: injection site pain, bruising, redness, reaction; knee stiffness, muscular weakness, spasms, synovitis, warmth; hip pain; dizziness; skin redness; rash; itching; back pain; headache; hypertension; swelling; effusion; migraine; contusion; burning sensation; increased blood liver enzyme, alkaline phosphatase, urea; and increased or decreased white blood cell count.

**How do I get more information about Gel-One®?**

If you have any questions or would like to find out more about Gel-One®, you may call xxx.

Manufactured by:

SEIKAGAKU CORPORATION
6-1, Marunouchi 1-chome, Chiyoda-ku
Tokyo 100-0005, Japan

Distributed by:

Zimmer Inc.
1800 West Center Street
Warsaw, Indiana, 46580, USA
Package Insert

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 77°F (25°C). 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.

**Table 1. Patient Baseline Characteristics – ITT Population**

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

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

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

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.

**Table 3. Adverse Events Related to Study Treatment**

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

**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.

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

![Diagram showing WOMAC Pain Subscore improvement from baseline at Week 13.](image)

Table 4. WOMAC\textsuperscript{a} VAS Pain Improvement from Baseline at 13 Weeks (ITT Population (N=375))\textsuperscript{b}

<table>
<thead>
<tr>
<th>Assessed Time-point</th>
<th>Model-Estimated Advantage (Gel-One\textsuperscript{®} - PBS)</th>
<th>Two-sided Lower 95% Confidence Limit (mm)</th>
<th>Two-sided P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>At Week 13</td>
<td>6.39 mm</td>
<td>0.37</td>
<td>0.0374</td>
</tr>
</tbody>
</table>

\textsuperscript{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.

\textsuperscript{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

<table>
<thead>
<tr>
<th>Odds Ratio$^b$</th>
<th>Two-sided Lower 95% Confidence Limit of Odds Ratio$^c$</th>
<th>Two-sided P-value$^d$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.27</td>
<td>0.85</td>
<td>0.2418</td>
</tr>
</tbody>
</table>

$^a$ 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

$\text{Log Odds Ratio} = \log_e \left[ \frac{\text{probability(responder)}}{\text{probability(non-responder)}} \right]_{\text{Gel-One}} / \left[ \frac{\text{probability(responder)}}{\text{probability(non-responder)}} \right]_{\text{PBS}}$

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

$^d$ Statistically not significant

### Table 6. Summary of Secondary Effectiveness$^a$ Endpoints at Week 13 – ITT Population

<table>
<thead>
<tr>
<th>Effectiveness Measures$^b$</th>
<th>Model-Estimated Advantage (Gel-One$^c$ - PBS)</th>
<th>Two-sided Lower 95% Confidence Limit (mm)</th>
<th>Two-sided P-value$^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total WOMAC Score</td>
<td>5.64 mm</td>
<td>-0.20</td>
<td>0.0583</td>
</tr>
<tr>
<td>WOMAC Stiffness</td>
<td>4.91 mm</td>
<td>-1.31</td>
<td>0.1216</td>
</tr>
<tr>
<td>WOMAC Physical Function</td>
<td>5.42 mm</td>
<td>-0.47</td>
<td>0.0714</td>
</tr>
</tbody>
</table>

$^a$ 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.
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 77°F (25°C). 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 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®.