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HYMOVIS® ONE

HYADD® 4 Viscoelastic Hyaluronan
For Intra-articular Injection

INSTRUCTIONS FOR USE

1 INFORMATION FOR PRESCRIBERS

HYMOVIS® ONE Viscoelastic Hyaluronan.

CAUTION:
Federal law restricts this device to sale by or on the order of a physician.

2 DESCRIPTION:

HYMOVIS® ONE is a sterile, non-pyrogenic, viscoelastic hydrogel contained in a single-use syringe. HYMOVIS® ONE is based on an ultra-pure, chemically modified hyaluronan (HYADD® 4), obtained using a proprietary process to increase viscosity, elasticity and residence time without chemical crosslinking. This results in a hyaluronan similar to the hyaluronan found in the synovial fluid present in the human joint. The hyaluronan in HYMOVIS® ONE is derived from bacterial fermentation.

3 INDICATIONS:

HYMOVIS® ONE 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 or simple analgesics (e.g., acetaminophen).

4 CONTRAINDICATIONS:

- Do not administer to patients with known hypersensitivity (allergy) to hyaluronate preparations.
- Do not administer to patients with known hypersensitivity (allergy) to gram positive bacterial proteins.
- Do not administer to patients with infections or skin diseases in the area of the injection site or joint.

5 WARNINGS:

- Do not use disinfectants containing quaternary ammonium salts for skin preparation prior to administration of HYMOVIS® ONE as hyaluronan can precipitate in their presence.
- Transient increases in inflammation following any intra-articular hyaluronan injection have been reported in some patients with inflammatory joint conditions.

6 PRECAUTIONS:

General

- Strict aseptic injection techniques should be employed during the administration of HYMOVIS® ONE.
- The safety and effectiveness of HYMOVIS® ONE in joints other than the knee have not been tested.
- The effectiveness of repeated treatment cycles of HYMOVIS® ONE has not been established.
- The safety and effectiveness of the use of HYMOVIS® ONE concomitantly with other intra- articular injections have not been established.
- STERILE CONTENTS. The pre-filled syringe is intended for single use only. The contents of the syringe are sterilized by moist steam and should be used immediately after opening. Discard any unused HYMOVIS® ONE. Do not re-sterilize.
- Do not use HYMOVIS® ONE if the package has been opened or damaged.
- HYMOVIS® ONE should be stored in its original package at a temperature between 2° to 25°C (36° to 77°F). DO NOT FREEZE.
- It is recommended to remove joint effusion, if present, before injecting HYMOVIS® ONE.
- Only properly licensed medical professionals trained in accepted injection techniques for delivering agents into the knee joint should inject HYMOVIS® ONE for the indicated use.
- Transient pain or swelling may occur after the intra-articular injection.
- It is recommended that patients avoid strenuous or prolonged (i.e., more than one hour) physical activities within 48 hours following the intra- articular injection.

7 USE IN SPECIFIC POPULATIONS

- **Pregnancy:** The safety and effectiveness of the use of HYMOVIS® ONE in pregnant women has not been tested.
- **Nursing Mothers:** It is not known if HYMOVIS® ONE is excreted in human milk. The safety and effectiveness of the use of the product in lactating women have not been tested.
- **Pediatrics:** The safety and effectiveness of the use of HYMOVIS® ONE have not been tested in children (21 years of age or younger).

8 POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH:

Potential adverse effects (e.g., complications) associated with the use of this type of device and, in general, associated with intra-articular injection for the treatment of pain in knee osteoarthritis, include: Infection, Arthralgia (knee pain), Arthrosis, Joint (knee) disorder, Joint (knee) swelling, Joint (knee) effusion, Joint (knee) stiffness, Pain in limb, Tendonitis, Paraesthesia, Phlebitis, Pruritus, Injection site erythema, Injection site edema, Injection site pain, Injection site reaction, Arthropathy, Baker's cyst, Bursitis, Localized osteoarthritis, Aggravated osteoarthritis, and Immune response.

Incidences of rash, headache, dizziness, chills, hives, nausea, muscle cramps, peripheral edema, and malaise have also been reported in association with intra-articular injections.

Reported Device-related Adverse Events
The adverse events experienced and reported in the HYMOVIS® ONE clinical study (EQE9-18-01) were joint swelling, metatarsalgia, neck pain and headache.

9 CLINICAL STUDIES

9.1 Study Design:
The HYMOVIS® ONE study (EQE9-18-01) was a multicenter, randomized, double-blinded, active comparator-controlled, non-inferiority study conducted in 18 centers in Italy to evaluate the safety and effectiveness of a single-injection regimen of HYMOVIS® ONE in patients with symptomatic osteoarthritis of the knee. This randomized controlled (RC) study was designed to evaluate the safety and effectiveness of HYMOVIS® ONE for the treatment of pain associated with symptomatic knee osteoarthritis with a 180-day (26 weeks) follow-up.

A total of 351 patients were enrolled in the RC study at 18 investigational sites, with 347 subjects randomized into two groups. Patients were randomized in a 1:1 ratio to either HYMOVIS® ONE or MONOVISC® injection. The objective of this study was to assess the effectiveness and safety of a single injection of HYMOVIS® ONE to relieve pain in the knee of patients with OA by establishing its non-inferiority to MONOVISC®, by evaluating changes from baseline in the WOMAC LK3.1 A1 pain subscale (walking on a flat surface) score at Week 12, as the primary endpoint, with additional follow-up of all outcome measures through Week 26.

The time from the first patient enrolled to completion of the last patient visit (last patient out) was approximately 19 months. The study was comprised of the following: a screening phase of 2 weeks, a single treatment visit, and a 26-week follow-up evaluation with visits at 1 week, 4 weeks, 12 weeks and 26 weeks post injection. Individual patient participation in the study lasted approximately 7 months.

Eligible patients were randomized into one of two treatment groups. The patient and the evaluator were blinded to the treatment group assignment. The treatment groups were:

Group 1:
- One single intra-articular injection of 4 mL (pre-filled syringes) HYMOVIS® ONE (8 mg/mL) on Day 0.

Group 2:
- One single intra-articular injection of 4 mL (pre-filled syringes) of MONOVISC® performed on Day 0.

9.2 Study Population:
The patients enrolled were female and male patients ≥ 40 and ≤ 75 years of age and diagnosed with OA of the knee based upon clinical and/or radiographic criteria of the American College of Rheumatology (Kellgren-Lawrence Score II-III) confirmed within three months prior to screening.

Patient exclusion criteria generally included conditions or medications that could confound the assessment of pain and conditions that could be adversely affected by an intra-articular injection. A total of 347 patients were randomized to either HYMOVIS® ONE (n=175) or MONOVISC® (n=172). Tables 1 and 2 summarize the baseline and patient demographic characteristics for the Safety Analysis Set and the baseline scores of the study respectively.

Table 1 Baseline and Patient Demographic Summary (Safety Analysis Set)

		HYMOVIS® ONE (n = 175)	MONOVISC® (n = 172)
Age (years)	n	175	172
	Mean (SD)	59.4 (8.68)	59.3 (8.38)
	Median	59.0	60.0
	Min / Max	40.0 / 78.0	40.0 / 75.0
	Q1 / Q3	53.0 / 65.0	53.0 / 65.0
Sex			
Male	n (%)	79 (45.1%)	89 (51.7%)
Female	n (%)	96 (54.9%)	83 (48.3%)
Race			
Caucasian	n (%)	174 (99.4%)	171 (99.4%)
Asian	n (%)	0 (0.0%)	0 (0.0%)
Black	n (%)	0 (0.0%)	1 (0.6%)
Other	n (%)	1 (0.6%)	0 (0.0%)
Height (m)	n	174	172
	Mean (SD)	1.70 (0.10)	1.70 (0.09)
	Median	1.69	1.70
	Min / Max	1.48 / 1.99	1.45 / 1.91
	Q1 / Q3	1.63 / 1.76	1.65 / 1.76
Height (inches)	n	174	172
	Mean (SD)	66.80 (3.88)	67.08 (3.49)
	Median	66.34	66.93
	Min / Max	58.27 / 78.35	57.09 / 75.20
	Q1 / Q3	64.17 / 69.29	64.96 / 69.29
BMI (kg/m2)	n	174	172
	Mean (SD)	26.31 (3.58)	26.58 (3.69)
	Median	25.75	26.11
	Min / Max	19.03 / 34.80	20.20 / 34.96
	Q1 / Q3	23.66 / 28.57	24.06 / 29.10
KL classification			
Grade 2	n (%)	126 (72.4%)	116 (67.4%)
Grade 3	n (%)	48 (27.6%)	56 (32.6%)

Table 2 Summary of Baseline Scores of the Study (Safety Analysis Set) (mean [SD])

	HYMOVIS® ONE (n=175)	MONOVISC® (n=172)
Walking Pain WOMAC A1	2.11 (0.44)	2.16 (0.41)
Pain WOMAC A	8.45 (2.83)	8.81 (2.67)
Stiffness WOMAC B	3.29 (1.71)	3.53 (1.55)
Function WOMAC C	26.57 (11.51)	28.30 (11.10)
Tegner activity level - n (%)		
3	88 (50.3%)	85 (49.4%)
4	53 (30.3%)	58 (33.7%)
5	24 (13.7%)	18 (10.5%)

9.3 Study Treatment and Evaluation Schedule
The patient follow-up period was 26 weeks. Study visits were scheduled for screening, baseline, and 1 week ±3 days, 4 weeks ±3 days, 12 weeks ±5 days, and 26 weeks ±7 days. Intra-articular injection was performed at the baseline visit (Day 0). Patients were required to discontinue all analgesics, including NSAIDs prior to the baseline visit and to accept "rescue" acetaminophen as the only medication for treatment of joint pain during the study. "Rescue" medication was not permitted within 24 hours of any study visit.

10 SAFETY RESULTS:

Safety analyses were performed for this study on the safety population, which was defined as all randomized patients who received the single injection study treatment. Treatment-emergent Adverse Events (TEAEs) were summarized by treatment group and categorized by severity and relationship to the study procedures.

A summary of all Adverse Events (AEs), including TEAEs and adverse device effects (ADEs), recorded in the Study is presented in Table 3 below. No serious TEAEs or ADEs were observed in the study.

Table 3 Summary of Adverse Events (Safety Analysis Set)

	HYMOVIS® ONE (N = 175) n (%) E	MONOVISC® (N = 172) n (%) E
Patients with at least one AE started before the date of randomization	10 (5.7%) 15	9 (5.2%) 17
Patients with at least one TEAE	51 (29.1%) 219	58 (33.7%) 348
Patients with at least one serious TEAE	0 (0.0%) 0	0 (0.0%) 0
Patients with at least one non-serious TEAE	51 (29.1%) 219	58 (33.7%) 348
Patients with at least one ADE	3 (1.7%) 4	5 (2.9%) 9
Patients with at least one serious ADE	0 (0.0%) 0	0 (0.0%) 0
Patients with at least one non-serious ADE	3 (1.7%) 4	5 (2.9%) 9
Patients with at least one TEAE leading to investigation discontinuation	0 (0.0%) 0	0 (0.0%) 0
Patients with at least one ADE leading to investigation discontinuation	0 (0.0%) 0	0 (0.0%) 0
Patients with at least one TEAEs leading to death	0 (0.0%) 0	0 (0.0%) 0
Patients with at least one ADE leading to death	0 (0.0%) 0	0 (0.0%) 0

n = number of patients; % = observed percentage;
E = number of events

The Treatment-Emergent Adverse Device Effects (TEADEs) most frequently reported are recorded in Table 4 below. Adverse Events were considered typical of viscosupplementation injections in this patient population and mostly were mild or moderate in severity.

HYMOVIS® ONE
HYADD® 4 Viscoelastic Hyaluronan For Intra-articular Injection

3002012/A

Table 4 Summary of Treatment-Emergent Adverse Device Effects (TEADE) by System Organ Class and Preferred Term (Safety Analysis Set)

System Organ Class Preferred Term	HYMOVIS® ONE (N=175) n (%) E	MONOVISC® (N=172) n (%) E
Patients with at least one ADE	3 (1.7%) 4	5 (2.9%) 9
General Disorders And Administration Site Conditions	0 (0.0%) 0	2 (1.2%) 2
Discomfort	0 (0.0%) 0	1 (0.6%) 1
Thirst	0 (0.0%) 0	1 (0.6%) 1
Musculoskeletal And Connective Tissue Disorders	3 (1.7%) 3	2 (1.2%) 3
Joint Contracture	0 (0.0%) 0	1 (0.6%) 1
Joint Swelling	1 (0.6%) 1	0 (0.0%) 0
Metatarsalgia	1 (0.6%) 1	0 (0.0%) 0
Myalgia	0 (0.0%) 0	1 (0.6%) 2
Neck Pain	1 (0.6%) 1	0 (0.0%) 0
Nervous System Disorders	1 (0.6%) 1	1 (0.6%) 2
Headache	1 (0.6%) 1	1 (0.6%) 2
Skin And Subcutaneous Tissue Disorders	0 (0.0%) 0	1 (0.6%) 1
Erythema	0 (0.0%) 0	1 (0.6%) 1
Surgical And Medical Procedures	0 (0.0%) 0	1 (0.6%) 1
Immunization	0 (0.0%) 0	1 (0.6%) 1

n = number of patients; % = observed percentage;
E = number of events

11 EFFECTIVENESS RESULTS

11.1 Primary Effectiveness Endpoint

The mean score of WOMAC LK3.1 A1 Walking Pain subscale decreased from baseline to Week 12 in both treatment groups. The mean (SD) change from baseline (CFB) to Week 12 was -1.38 (0.82) (median change -2.00, range from -3.00 to 1.00) in the HYMOVIS® ONE group and -1.42 (0.81) (median change -1.00, range from -3.00 to 1.00) in the MONOVISC® group.

An inferential statistical analysis was performed on the primary effectiveness endpoint using the approach of the multiple imputation to address the missing values. The baseline WOMAC LK3.1 A1 Walking Pain, patient's age, and Kellgren-Lawrence (K-L) grade were considered as covariates. The adjusted means (LSM) were -1.327 and -1.353 for HYMOVIS® ONE and MONOVISC®, respectively.

The adjusted means difference was 0.026 [95% CI: -0.1334 to 0.1849]. The difference between the two groups was not statistically significant (p = 0.7486). As the upper limit of the 95% CI of the difference of LSM of Test and Reference at Week 12 was lower than the non-inferiority margin of 0.32, HYMOVIS® ONE resulted to be non-inferior to MONOVISC® (p = 0.0003 in the test for non-inferiority). No statistically significant treatment by site effect was observed (p = 0.5669).

The same findings were observed in the analysis performed using roll back and last observation carried forward (LOCF) imputation for the missing values, as well as in the PP population: all analyses did not show statistically significant differences between groups and confirmed that HYMOVIS® ONE was non-inferior to MONOVISC® in the primary effectiveness endpoint. See Tables 5 and 6 below for a summary of the WOMAC LK3.1 A1 Walking Pain subscale from baseline to Week 26. The results of CFB to Week 12 of WOMAC LK3.1 A1 Walking Pain subscale in the PP population were consistent with those observed in the ITT population.

Table 5 Summary of results of WOMAC LK3.1 A1 Walking Pain subscale using multiple imputation (ITT population)

	HYMOVIS® ONE (N = 175)	MONOVISC® (N = 172)
Baseline	2.11 ± 0.44 (N=175)	2.16 ± 0.41 (N=172)
Changes from baseline		
Week 4	-1.19 ± 0.78 (N=175)	-1.19 ± 0.83 (N=172)
Week 12	-1.38 ± 0.82 (N=175)	-1.42 ± 0.81 (N=172)
Week 26	-1.54 ± 0.82 (N=175)	-1.49 ± 0.86 (N=172)

Values are mean ± SD; n = number of patients

Table 6 Summary of results of WOMAC LK3.1 A1 Walking Pain subscale A (PP population)

	HYMOVIS® ONE (N = 154)	MONOVISC® (N = 156)
Baseline	2.10 ± 0.31 (N=154)	2.17 ± 0.38 (N=156)
Changes from baseline		
Week 4	-1.20 ± 0.74 (N=154)	-1.21 ± 0.81 (N=156)
Week 12	-1.38 ± 0.78 (N=154)	-1.46 ± 0.77 (N=156)
Week 26	-1.57 ± 0.74 (N=154)	-1.53 ± 0.84 (N=156)

Values are mean ± SD; n = number of patients

11.2 Secondary Effectiveness Endpoints

Patient success (OMERACT-OARSI)

Patient success was achieved at Week 12 in 152 HYMOVIS® ONE patients (86.9%; 95% CI: 80.9 to 91.5%) and in 140 MONOVISC® patients (81.4%; 95% CI: 74.8 to 86.9%) and at Week 26 in 151 HYMOVIS® ONE patients (86.3%; 95% CI: 80.3 to 91.0%) and in 147 MONOVISC® patients (85.5%; 95% CI: 79.3 to 90.4%). The difference between groups was not statistically significant.

Change from Baseline (CFB) in WOMAC LK3.1 Pain Subscale

The mean score of WOMAC LK3.1 Pain subscale decreased from baseline to any post-treatment timepoint in both groups. The mean (SD) change from baseline to Week 4 was -4.16 (2.91) in the HYMOVIS® ONE group and -4.28 (3.28) in the MONOVISC® group; the mean (SD) change from baseline to Week 12 was -5.16 (3.34) in the HYMOVIS® ONE group and -5.13 (3.60) in the MONOVISC® group; and the mean (SD) change from baseline to Week 26 was -5.54 (3.61) in the HYMOVIS® ONE group and -5.30 (3.88) in the MONOVISC® group. The comparison between groups showed that the adjusted mean difference between the HYMOVIS® ONE group and the MONOVISC® group was -0.091 (95% CI: -0.7228 to 0.5407) at Week 4, 0.262 (95% CI: -0.8977 to 0.3735) at Week 12, -0.508 (95% CI: -1.1395 to 0.1243) at Week 26, and -0.287 (95% CI: -0.6534 to 0.0795) in the overall investigation period. The comparison between groups did not show statistically significant differences at any post-baseline time point and in the overall investigation period.

CFB in WOMAC LK3.1 Stiffness Subscale

The mean score of WOMAC LK3.1 Stiffness subscale decreased from baseline to any post-treatment time point in both treatment groups. The comparison between groups did not show statistically significant differences at any post-baseline time point and in the overall investigation period. The extent of the mean decrease from baseline to any post-baseline time point of WOMAC LK3.1

CFB in WOMAC LK3.1 Function Subscale

The mean score of WOMAC LK3.1 Function subscale progressively decreased from baseline to any post-treatment timepoint in both treatment groups. The comparison between groups did not show statistically significant differences at 4 and 12 Weeks post-treatment. At Week 26, the mean (SD) change from baseline was -16.26 (12.03) in the HYMOVIS® ONE group and -15.24 (13.68) in the MONOVISC® group with an adjusted means difference between the HYMOVIS® ONE group and the MONOVISC® group of -2.244 (95% CI: -4.3487 to -0.1384). The comparison between groups showed, a statistically significant difference at 26 Weeks post-treatment (p = 0.0367) in favor of the HYMOVIS® ONE group.

Short-Form (SF)-12 Questionnaire

Physical Component Summary (PCS)

The mean score of PCS progressively improved from baseline to any post-treatment timepoint for both groups. There were no statistical differences between the groups at any post-treatment timepoint. The mean change (SD) from baseline

- to Week 4 was 3.83 (7.20) in HYMOVIS® ONE patients and 4.58 (7.25) in MONOVISC® patients
- to Week 12 was 4.77 (7.77) in HYMOVIS® ONE patients and 5.29 (8.04) in MONOVISC® patients
- to Week 26 was 6.29 (7.79) in HYMOVIS® ONE patients and 5.76 (8.54) in MONOVISC® patients

Mental Component Summary (MCS)

The mean score of MCS improved from baseline to any post-treatment timepoint for both groups. There were no statistical differences between the groups at any post-treatment timepoint. The mean (SD) change from baseline

- to Week 4 was 1.52 (7.50) in HYMOVIS® ONE patients and 1.60 (7.85) in MONOVISC® patients
- to Week 12 was 1.92 (8.98) in HYMOVIS® ONE group and 2.47 (8.19) in MONOVISC® patients
- to week 26 was 1.76 (8.78) in HYMOVIS® ONE group and 2.07 (9.12) in MONOVISC® patients.

Patient Global Assessment (PGA) of disease activity and of Clinical Observed Global Assessment (COGA) of disease severity

The mean score of PGA of disease activity and of COGA of disease severity progressively improved from baseline to any post-treatment timepoint for both groups, with similar improvements observed in both groups. The comparison between groups did not show statistically significant differences at any post-treatment timepoint and in the overall investigation period for both endpoints. Similar results were also observed for the two groups at any post-treatment timepoint with respect to in improvements ≥ 30%, ≥ 40% and ≥ 50% from baseline.

Use of rescue medication (acetaminophen)

The number of patients that used rescue medication was 134 (76.6%) in the HYMOVIS® ONE group and 136 (79.1%) in the MONOVISC® group. The comparison between groups of total amount of rescue medication used was not statistically significant. A similar proportion of patients in the two groups used rescue medication.

12 BENEFIT-RISK ANALYSIS

One single intra-articular injection of HYMOVIS® ONE provides benefit in pain reduction in patients with knee osteoarthritis that is non-inferior to the pain reduction provided by one single intra-articular injection of MONOVISC®, a product previously approved for the same indication. Safety assessment results support a favorable benefit/risk ratio; that is, the probable benefits outweigh the probable risks of transitory adverse events such as pain in the treatment of knee osteoarthritis in patients who have failed to adequately respond to conservative non-pharmacological therapy and simple analgesics (e.g., acetaminophen).

13 DETAILED DEVICE DESCRIPTION

HYMOVIS® ONE is a proprietary hyaluronic acid (HA) based viscosupplement intended for the treatment of pain in patients with osteoarthritis (OA) of the knee who have failed conservative non-pharmacological therapy and simple analgesics. The device is administered as a single injection regimen under aseptic conditions.

HYMOVIS® ONE is engineered by modification of hyaluronan (hyaluronic acid) with a proprietary process without chemical crosslinking and results in a highly viscoelastic hydrogel called HYADD®4 with increased lubricating and shock absorption properties. The HA is derived from bacterial fermentation *(Streptococcus equi)*.

14 HOW SUPPLIED

HYMOVIS® ONE has a hyaluronan (HYADD®4) concentration of 8 mg/mL, dissolved in physiologic saline. HYMOVIS® ONE is supplied in a 5.0 mL syringe containing 4.0 mL of HYMOVIS® ONE. The contents of the syringe are sterile and non-pyrogenic. Each syringe is labeled HYMOVIS® ONE for ready identification. The syringe components contain no latex.

15 DIRECTIONS FOR USE

HYMOVIS® ONE is intended to be injected into the knee joint and is administered as a single intra- articular injection regimen. Standard intra-articular injection site preparation and strict aseptic administration techniques must be followed.

1. Using an 18 – 20 gauge needle, it is recommended to remove synovial fluid or effusion before injecting HYMOVIS® ONE. Do not use the same syringe for removing synovial fluid and for injecting HYMOVIS® ONE; however, the same 18 – 20 gauge needle can be used.
2. While firmly holding the luer-lock hub, remove the protective rubber cap on the tip of the syringe (Fig. 1). By twisting the tip cap (Fig. 2) before pulling it off (Fig. 3), as this will minimize product leakage.
3. To ensure a tight seal and prevent leakage during administration, secure the 18 - 20 gauge needle (Fig. 4) tightly while firmly holding the luer hub (Fig. 5). Take care not to rotate the hub during needle attachment which can lead to loosening of the hub. Do not overtighten or apply excessive leverage when attaching the needle or removing the needle guard (Fig 6), as this may break the syringe tip.
4. Inject the full 4 mL in one knee only (do not overfill the joint). If treatment is bilateral, a separate syringe should be used for each knee.

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