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SOLUTIONS

HYMOVIS® (German) Product Specifications

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HYMOVIS®
HYADD®4 High Molecular Weight Viscoelastic Hyaluronan

INSTRUCTIONS FOR USE

1 INFORMATION FOR PRESCRIBERS
HYMOVIS® High Molecular Weight Viscoelastic Hyaluronan

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

2 DESCRIPTION:
HYMOVIS® is a sterile, non-pyrogenic, viscoelastic hydrogel contained in a single-use syringe. HYMOVIS® is based on an ultra-pure hyaluronan engineered using a proprietary process to increase viscosity, elasticity and residence time without chemical crosslinking. This results in a natural hyaluronan similar to the hyaluronan found in the synovial fluid present in the human joint. The hyaluronan in HYMOVIS® is derived from bacterial fermentation.

3 INDICATIONS:
HYMOVIS® 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® 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 technique should be employed during the administration of HYMOVIS®.
- The safety and effectiveness of the HYMOVIS® in joints other than the knee have not been tested.
- The effectiveness of repeat treatment cycles of HYMOVIS® has not been established.
- The safety and effectiveness of the use of HYMOVIS® concomitantly with other intra-articular injections have not been established.
- STERILE CONTENTS. The pre-filled syringes are 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®. Do not re-sterilize.
- Do not use HYMOVIS® if the package has been opened or damaged.
- HYMOVIS® should be stored in its original package at room temperature (below 77°F/25°C). DO NOT FREEZE.
- It is recommended to remove joint effusion, if present, before injecting HYMOVIS®.
- Only properly licensed medical professionals trained in accepted injection techniques for delivering agents into the knee joint should inject HYMOVIS® 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® in pregnant women has not been tested.
- **Nursing Mothers:** It is not known if HYMOVIS® is excreted in human milk. The safety and effectiveness of the use of the product in lactating women has not been tested.
- **Pediatrics:** The safety and effectiveness of the use of HYMOVIS® 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 devices for the treatment of pain in osteoarthritis of the knee, include: infection, arthralgia (knee pain), arthrosis, joint disorder, joint swelling, joint effusion, joint 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 most commonly reported adverse event associated with intra-articular injection was arthralgia. The incidence of arthralgia in the clinical study for HYMOVIS® was equivalent for the HYMOVIS® and control groups. No serious adverse reactions or pseudoseptic reactions were reported.

9 CLINICAL STUDIES
9.1 Study Design:
The original HYMOVIS® R29-09-02 study was a randomized, double- blinded, phosphate-buffered saline-controlled study conducted at 37 centers in U.S. to evaluate the safety and effectiveness of a two-injection regimen of HYMOVIS® in patients with symptomatic osteoarthritis of the knee. This randomized controlled (RC) study was designed to evaluate the safety and effectiveness of a new viscoelastic hydrogel (HYMOVIS®) for the treatment of pain associated with symptomatic osteoarthritis of the knee with a 180- day (26 weeks) follow-up with an additional 90-day (12 weeks) open label extension (OLE) phase for the evaluation of safety of one cycle of repeat treatment.

A total of 800 patients were enrolled in the RC study and 529 patients in the OLE study phase. Patients were randomized in a 1:1 ratio to either HYMOVIS® or phosphate-buffered saline injection. The primary endpoint was to determine the superiority of HYMOVIS® compared to phosphate-buffered saline by evaluating the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) in WOMAC VAS Pain Score (WOMAC A, 100mm scale) absolute improvement from baseline at Week 26 (180 days).

9.1.1 Randomized Controlled (RC) Study Phase
For the randomized controlled phase of the original HYMOVIS® RC study, a total of 801 were randomized and 800 received treatment at 37 Investigator sites. The time from the first patient enrolled to completion of the last patient visit (last patient out) was approximately 20 months. Individual patient participation lasted approximately nine months (six months for the randomized phase, and three additional months if the patient opted for the OLE phase).

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:
- Two intra-articular injections of 3 mL (pre-filled syringes) HYMOVIS® (8 mg/mL); one injection on Day 0 and the second on Day 7;

Group 2:
- Two intra-articular injections of 3 mL (pre-filled syringes) of phosphate-buffered saline given on Day 0 and the second on Day 7.

9.1.2 Open Label Extension (OLE) Study Phase
After completion of all safety and efficacy assessments at the Day 180 (Week 26) Visit for the original HYMOVIS® RC study, patients were offered the opportunity to further participate in an open label extension phase of the study for the evaluation of safety of one cycle of repeat treatment. The duration of the OLE phase was 90 days beyond receiving repeat treatment.

Eligible patients were summarized based on the injections that they received in the randomized study phase. Treatment groups were as follows:

Group 1:
- Patient received HYMOVIS® in the randomized study phase, known as the 2nd HYMOVIS® group for the OLE study phase. Two intra-articular injections of 3 mL (pre-filled syringes) HYMOVIS® (8 mg/mL) were administered by qualified personnel other than the Blinded Investigator/Observer, at repeat Day 0 and at repeat Day 7.

Group 2:
- Patients received phosphate-buffered saline in the randomized study phase, known as the 1st HYMOVIS® group for the OLE study phase. Two intra- articular injections of 3 mL (pre-filled syringes) HYMOVIS® (8 mg/mL) were administered by qualified personnel other than the Blinded Investigator/ Observer, at repeat Day 0 and at repeat Day 7.

Results from the OLE study phase were used for the safety profile, but not in the assessment of effectiveness.

9.2 Study Population:
The patients enrolled in the original RC study were > 40 years old 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 800 patients were randomized to either HYMOVIS® (n=400) or phosphate-buffered saline (n=400). These 800 patients comprised the Safety Population (Full Analyses Set). Table 1 summarizes the baseline and patient demographic characteristics for Full Analyses Set population.

Table 1 Baseline and Patient Demographic Summary of RC Study

Patient Screening Characteristics	HYMOVIS® (N=400)	Phosphate-buffered saline (N=400)	All Patients (N=800)
Mean of Age (years) (SD)	60.9 (10.3)	60.3 (9.77)	60.6 (9.90)
Gender [N (%)]			
Male	175 (43.8)	157 (39.3)	332 (41.5)
Female	225 (56.3)	243 (60.8)	468 (58.5)

9.3 Study Treatment and Evaluation Schedule
RC Study Phase
The patient follow-up period for the RC Study Phase was 180 Days (26 weeks). Study visits were scheduled for screening, baseline, and Days 7, 14, 28, 60, 90, 120 and 180. Injections were performed at the baseline visit and Day 7 visit. 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.

OLE Study Phase
During the Open-Label Extension Study Phase, the follow-up visits were scheduled at Day 7, Day 14 and Day 90 following fist injection of the retreatment cycle.

10 SAFETY RESULTS:
Safety analyses were performed for this study on the safety population, which was defined as all randomized patients of the original RC Study Phase and the Open Label Extension (OLE) Study Phase. Treatment-emergent Adverse Events (AEs) were summarized by treatment group and categorized by severity and relationship to the study procedures.

To assess the safety of a repeat injection regimen of two 3 mL of HYMOVIS® the compliant patients from both arms were permitted to enter a 90 day open-label repeat treatment phase after the completion of the initial study injection regimen.

10.1 RC Study Phase
A summary of AEs recorded in the RC Study Phase is presented in Table 2 below.

Table 2 Summary of Adverse Events (Safety Analysis Set) of the RC Study Phase

	HYMOVIS® (N=400) n (%)	Phosphate-buffered saline (N=400) n (%)	Overall (N=800) n (%)
Patients with at least one Adverse Event	187 (46.8)	182 (45.5)	369 (46.1)
Patients with at least one Treatment Emergent Adverse Event	184 (46.0)	180 (45.0)	364 (45.5)
Treatment Emergent Adverse Events	358	353	711
Patients with at least one Treatment Emergent Adverse Device Effect	17 (4.3)	19 (4.8)	36 (4.5)
Patients with AEs that led to discontinuation of participation in the study	0	1 (0.3)	1 (0.1)

Table 3 Patients in RC Study with Treatment Emergent Adverse Events by Degree of Severity

Mild	88 (22.0)	90 (22.5)	178 (22.3)
Moderate	78 (19.5)	69 (17.3)	147 (18.4)
Severe	18 (4.5)	21 (5.3)	39 (4.9)

The treatment-emergent adverse events 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.

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

System Organ Class Preferred Term	HYMOVIS® (N=400) n (%)	Phosphate-buffered saline (N=400) n (%)	Overall (N=800) n (%)
Number of Patients With At Least One TEADE	17 (4.3)	19 (4.8)	36 (4.5)
General disorders and administration site conditions	2 (0.5)	5 (1.3)	7 (0.9)
Injection site discomfort	0	1 (0.3)	1 (0.1)
Injection site erythema	1 (0.3)	2 (0.5)	3 (0.4)
Injection site pain	1 (0.3)	3 (0.8)	4 (0.5)
Injection site pruritus	1 (0.3)	1 (0.3)	2 (0.3)
Injury, poisoning and procedural complications	0	1 (0.3)	1 (0.1)
Contusion	0	1 (0.3)	1 (0.1)
Musculoskeletal and connective tissue disorders	15 (3.8)	12 (3.0)	27 (3.4)
Arthralgia	7 (1.8)	7 (1.8)	14 (1.8)
Haemarthrosis	0	1 (0.3)	1 (0.1)
Joint crepitation	0	1 (0.3)	1 (0.1)
Joint effusion	0	2 (0.5)	2 (0.3)
Joint instability	0	1 (0.3)	1 (0.1)
Joint lock	1 (0.3)	1 (0.3)	2 (0.3)
Joint stiffness	4 (1.0)	1 (0.3)	5 (0.6)
Joint swelling	4 (1.0)	3 (0.8)	7 (0.9)
Sensation of heaviness	1 (0.3)	0	1 (0.1)
Nervous system disorders	1 (0.3)	0	1 (0.1)
Sensory disturbance	1 (0.3)	0	1 (0.1)
Skin and subcutaneous tissue disorders	0	1 (0.3)	1 (0.1)
Pruritus	0	1 (0.3)	1 (0.1)

10.2 Open-Label Extension (OLE) Study Phase

A summary of Adverse Events recorded in the OLE Study Phase is presented in Table 5 below.

Table 5 Summary of Treatment-Emergent Adverse Device Effects by System Organ Class and Preferred Term (Safety Analysis Set) for OLE Study

System Organ Class Preferred Term	2nd HYMOVIS® (N=257)	1st HYMOVIS® (N=272)	Overall (N=529)
Number of Patients With At Least One TEADE	18 (7.0)	12 (4.4)	30 (5.7)
General disorders and administration site conditions	1 (0.4)	1 (0.4)	2 (0.4)
Inflammation	0	1 (0.4)	1 (0.2)
Injection site pain	1 (0.4)	0	1 (0.2)
Immune system disorders	1 (0.4)	0	1 (0.2)
Hypersensitivity	1 (0.4)	0	1 (0.2)
Infections and infestations	1 (0.4)	0	1 (0.2)
Arthritis bacterial	1 (0.4)	0	1 (0.2)
Injury, poisoning and procedural complications	0	1 (0.4)	1 (0.2)
Contusion	0	1 (0.4)	1 (0.2)
Musculoskeletal and connective tissue disorders	15 (5.8)	11 (4.0)	26 (4.9)
Arthralgia	13 (5.1)	9 (3.3)	22 (4.2)
Arthritis	1 (0.4)	0	1 (0.2)
Joint effusion	2 (0.8)	1 (0.4)	3 (0.6)
Joint stiffness	1 (0.4)	1 (0.4)	2 (0.4)
Joint swelling	1 (0.4)	2 (0.7)	3 (0.6)
Osteoarthritis	0	1 (0.4)	1 (0.2)

11 EFFECTIVENESS RESULTS

11.1 RC Study Phase

PRIMARY EFFECTIVENESS ENDPOINT

The analysis of the effectiveness of HYMOVIS® was based on the modified Full Analysis Set (mFAS) population (n=786 patients) evaluable at the 6-month time point. The pain reduction from baseline for HYMOVIS® was -19.47 mm on the whole 100 mm WOMAC A Pain scale and that of phosphate-buffered saline (PBS) was -18.13 mm. The primary effectiveness endpoint was not met in this study. As shown below in Table 6, the study did not demonstrate a statistically significant difference, as well as a clinically meaningful difference of at least 6 mm, between the two groups in WOMAC A Pain Scores at six months.

Table 6 WOMAC A Pain Reduction from Baseline – Modified Full Analysis Set (mFAS) Population (n=786) at 180 Days

Treatment	Baseline	Changes from Baseline WOMAC Score	Model-Estimated Advantage (HYMOVIS®-PBS)	95% CI Lower and Upper Bound (mm)	P-value
HYMOVIS® (n=393)	57.28	-19.47	-1.39	(-3.74, 0.96)	0.25
Phosphate-buffered saline (n=393)	57.18	-18.13			

The analysis was based on a two-sided t-test at 180 days for the primary endpoint.

SECONDARY EFFECTIVENESS ENDPOINTS

All secondary endpoints shown below were not statistically different from Phosphate-buffered saline.

- Responder, based on OMERACT-OARSI*, at 26 weeks
- Function measured in WOMAC C
- VAS pain measured in WOMAC A 1 (Pain subscore)
- WOMAC Global Score
- Stiffness measured in WOMAC B

*Outcome Measures in Rheumatology Clinical Trials and Osteoarthritis Research Society International (OMERACT-OARSI) criteria of response

11.2 HYMOVIS® vs. HYALGAN® (Sodium Hyaluronate) Post Hoc Non-Inferiority Analysis

The primary effectiveness endpoint for the HYMOVIS® pivotal RC study (R29-09-02), comparison of the reductions in the WOMAC Pain Score (WOMAC A) from baseline through 180 days, was used for a post-hoc non-inferiority comparison of HYMOVIS® to HYALGAN®, previously approved under P950027 for an identical indication for use. WOMAC A Pain Scores were utilized to determine the non-inferiority of HYMOVIS® to HYALGAN® using Bayesian regression analysis. Under this Bayesian analysis, a two-injection treatment regimen of HYMOVIS® was assessed for its ability to provide pain relief non-inferior to that of a 5-injection treatment regimen of HYALGAN® as determined through comparison of the reduction in WOMAC A Pain Scores from baseline through 180 days utilizing a non-inferiority margin of 5 mm on the 100mm WOMAC A Pain Scale.

The primary effectiveness endpoint for this non-inferiority analysis was met as calculated using a Bayesian regression analysis with posterior probability of 97%.

11.3 Non-Inferiority Endpoints

The non-inferiority margins were set conservatively at Δ=5 mm (on a 100mm WOMAC VAS Scale), 10 mm for Patient Global Assessment, and a 0.8 relative risk for the OMERACT-OARSI response rate.

The mean differences between treatment groups are calculated and a lower one-sided 97.5% confidence interval is constructed. If the lower bound is greater than -Δ, then 'Non-inferiority' is obtained for HYMOVIS® relative to the five-injection HYALGAN® group.

11.4 Clinical Significance Demonstration

To demonstrate clinical significance, a cumulative distribution method for determining of the change from baseline for each of the endpoints was employed. Cumulative Distribution Function (CDF) plots comparing the HYMOVIS® two injection regimen to the HYALGAN® five-injection regimen effectiveness were conducted and provided for primary and secondary endpoints. At -6.0 mm on a 100mm WOMAC VAS scale, which is considered a valid clinically important difference, the CDF plots demonstrate that HYMOVIS® demonstrates a higher degree of clinical improvement than HYALGAN® for all significant test endpoints.

Figures 1 and 2 below show the Cumulative Distribution Plot for Change in WOMAC A Pain Score from Baseline to Day 120 and Day 180.

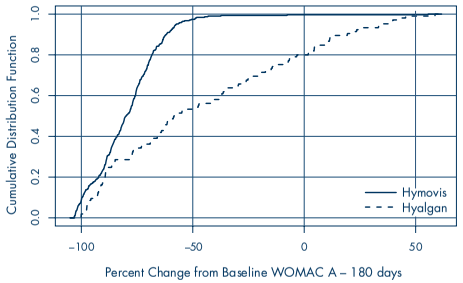

Figure 1 Cumulative Distribution Function for Percent Change in WOMAC A at Day 180

The CDF curves for the endpoints (WOMAC Pain Score at day 180) show that the HYMOVIS® mPP population demonstrates a higher degree of clinical improvement at day 180 to HYALGAN®.

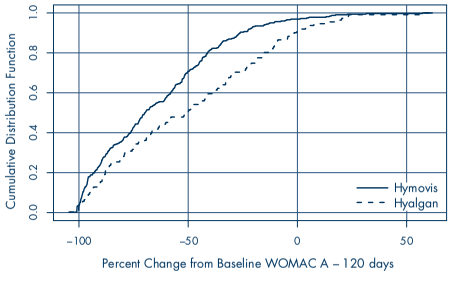

Figure 2 Cumulative Distribution Function for Percent Change in WOMAC A at Day 120

The CDF curves for the endpoints (WOMAC Pain Score at day 120) show that the HYMOVIS® population demonstrates a higher degree of clinical improvement at day 120.

12 BENEFIT-RISK ANALYSIS

Two injections of HYMOVIS® provide a benefit in pain reduction in patients with osteoarthritis in the knee that is non-inferior to the pain reduction provided by 5 injections of HYALGAN®, a product previously approved for the same indications. 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 osteoarthritis of the knee in patients who have failed to adequately respond to conservative non-pharmacological therapy and simple analgesics (e.g., acetaminophen).

13 DETAILED DEVICE DESCRIPTION

HYMOVIS® is a proprietary high molecular weight hyaluronic acid-based viscosupplementation 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 two-injection regimen under aseptic conditions.

HYMOVIS® has a hyaluronan (HYADD®4) concentration of 8 mg/mL, dissolved in physiologic saline. It is supplied in a 5.0 mL syringe containing 3.0 mL of HYMOVIS®. The contents of the syringe are sterile and non-pyrogenic.

HYMOVIS® 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 hyaluronic acid is derived from bacterial fermentation *(Streptococcus equi)*.

14 HOW SUPPLIED

HYMOVIS® is supplied in a set of 2 single-use 5 mL syringes, each containing a 3 mL dose of treatment to be injected one week apart. Each syringe is labeled Hymovis® for ready identification. The contents of the syringe are sterile and non-pyrogenic. The syringe components contain no latex.

15 DIRECTIONS FOR USE

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

1. Using an 18 – 20 gauge needle, it is recommended to remove synovial fluid or effusion before injecting HYMOVIS®. Do not use the same syringe for removing synovial fluid and for injecting HYMOVIS®; however, the same 18 – 20 gauge needle can be used.
2. While firmly holding the luer hub, remove the protective rubber cap on the tip of the syringe (Fig. 1). By twist 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 (Fig. 5). 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 3 mL in one knee only (do not overfill the joint). If treatment is bilateral, a separate syringe should be used for each knee.
5. Administer the second injection of HYMOVIS® in the same joint in a week after the first injection following the same guidelines.

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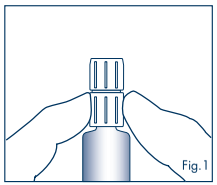
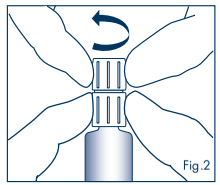


Fig.1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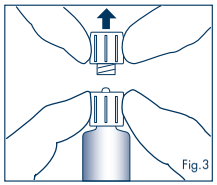
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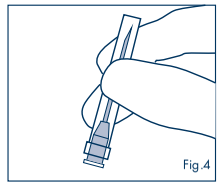
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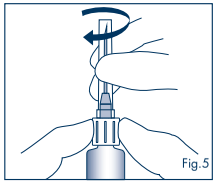
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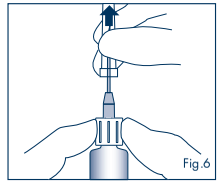
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