

TriVisc™

(sodium hyaluronate)

Full Prescribing Information

CAUTION

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

DESCRIPTION

TriVisc™ is a sterile, viscoelastic non-pyrogenic solution of purified, high molecular weight sodium hyaluronate. Each 2.5 mL of TriVisc contains 10mg/mL of sodium hyaluronate dissolved in a physiological saline. The sodium hyaluronate is derived from bacterial fermentation. Sodium hyaluronate is a poly-saccharide containing repeating disaccharide units of glucuronic acid and N-acetylglucosamine.

INDICATIONS AND USAGE

TriVisc 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 and simple analgesics, e.g., acetaminophen.

CONTRAINDICATIONS

- Do not administer to patients with known hypersensitivity (allergy) to sodium hyaluronate preparations.
- Do not inject this product in the knees of patients with infections or skin diseases 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.

PRECAUTIONS

- Remove joint effusion, if present, before injecting TriVisc.
- Do not use TriVisc if the package is opened or damaged. Store in the original packaging (protected from light) below 86°F (30°C). DO NOT FREEZE. Do not use after expiration date indicated on package. The shelf life of TriVisc is 42 months.
- The effectiveness of a single treatment cycle of less than 3 injections has not been established.
- Transient increases in inflammation following any intra-articular hyaluronan injection have been reported in some patients with inflammatory joint conditions.
- The effectiveness of repeat treatment cycles of TriVisc has not been established.

- Strict aseptic administration technique must be followed to avoid infections in the injection site.
- The safety and effectiveness of the use of TriVisc in joints other than the knee have not been established.
- The safety and effectiveness of the use of TriVisc concomitantly with other intra-articular injectable products have not been established.

STERILE CONTENTS

The prefilled syringe is intended for single use. The contents of the syringe must be used immediately once the container has been opened. Discard any unused TriVisc.

INFORMATION FOR PATIENTS

- Provide patients with a copy of the Patient Information prior to use.
- Transient pain and/or swelling of the injected joint may occur after intra-articular injection of TriVisc.
- As with any invasive joint procedure, it is recommended that the patient avoid any strenuous activities or prolonged (i.e., more than 1 hour) weight-bearing activities such as jogging or tennis within the 48 hours that follow the intra-articular injection.

Use in Specific Populations

- **Pregnancy:** The safety and effectiveness of TriVisc have not been established in pregnant women.
- **Nursing Mothers:** It is not known if TriVisc is excreted in human milk. The safety and effectiveness of TriVisc have not been established in lactating women.
- **Pediatrics:** The safety and effectiveness of TriVisc have not been demonstrated in children (21 years of age or younger).

ADVERSE EVENTS

The primary clinical performance testing to assess the safety of TriVisc were two clinical studies, the AMELIA¹ and Yong Ping² studies, used to establish reasonable assurance of the safety of established in the approval of another intra-articular hyaluronan (HA) under P140005³ (P140005 HA). TriVisc is of identical chemical formulation to this HA and differs only in that less of the device is injected (3 weekly injections of 2.5 ml for TriVisc instead of 5 weekly injections). Thus, the clinical studies used to provide evidence of the reasonable assurance of the safety of the HA under P140005 are directly applicable to TriVisc as well.

The primary evidence of the safety under P140005 was provided by the comparison of the P140005 HA to PBS in the AMELIA study. In this study, four cycles of 5 injections of the

¹ Navarro-Sarabia F, Coronel P, Collantes E, Navarro FJ, de la Serna AR, Naranjo A, Gimeno M, Herrero-Beaumont G; AMELIA study group. A 40-month multicentre, randomised placebo-controlled study to assess the efficacy and carry-over effect of repeated intra-articular injections of hyaluronic acid in knee osteoarthritis: the AMELIA project. *Ann Rheum Dis*. 2011;70: 1957-62.

² Y., Jianhao, L., Tiansheng, S., Yongqiang, H., Weimin, F., Ming, C., Tiezheng, S., Jianhua, Y., Liang, X., Xiaoyuan, G., Yongping, C., 2016. The efficacy and safety of sodium hyaluronate injection (Adant(R)) in treating degenerative osteoarthritis: a multi-center, randomized, double-blind, positive-drug parallel-controlled and non-inferiority clinical study. *Int J Rheum Dis* 19, 271–278.

³ Summary of Safety and Effectiveness Data (SSED)-GenVisc 850 https://www.accessdata.fda.gov/cdrh_docs/pdf14/P140005B.pdf

P140005 HA or PBS were administered with an interval of 6 months for the first three cycles, and 1 year for the fourth cycle. Patients were followed for 1 year after the last injection. The population of patients evaluated for the safety of the P140005 HA included 306 subjects (153 HA, 153 PBS). In each treatment group, 127 subjects experienced at least one adverse event during the study, and 22 patients (11 in each treatment group) experienced at least one adverse event that was reported as possibly, probably or certainly related to the device (4). None of the related adverse events were assessed as severe. In the HA treatment group, the 15 adverse events reported as related adverse events were pain at the injection site (6), allergic reaction (3), arthralgia (2), bleeding at the injection site (2), bleeding (1), and heaviness (1). In the PBS treatment group, the 14 adverse events reported as related were bleeding at the injection site (6), allergic reaction (3), pain at the injection site (2), arthralgia (1), and arthritis (1).

Table 1: Related adverse events by severity

Related Adverse Events	HA under P140005			PBS		
	Mild	Moderate	Total	Mild	Moderate	Total
Allergic reaction	2	1	3	3	--	3
Pain injection site	2	4	6	2	--	2
Bleeding	--	1	1	--	--	--
Bleeding at injection site	2	--	2	6	--	6
Arthralgia	--	2	2	1	1	1
Arthritis	--	--	--	--	1	1
Heaviness	1	--	1	--	--	--
Total	7	8	15	12	2	14

A total of 513 complete P140005 HA treatment cycles and a total of 487 complete PBS treatment cycles were administered in the study. Table 2 provides the number of related adverse events per complete treatment cycle. The rate of adverse events per treatment cycle for HA is 0.029, which is the same as the PBS rate. This low adverse event rate demonstrates the safety of the P140005 HA following repeat treatments.

Table 2: Related adverse events by treatment cycles

Treatment	No. Complete Cycles	No. Related Adverse Events	Related AEs per Complete Cycles
P140005 HA	513	15	0.029
PBS	487	14	0.029

Supporting evidence of safety is provided by the comparison of P140005 HA to an approved HA under P980044⁴ in the Yong Ping study for time periods up to 6 weeks. The population of patients evaluated to assess the safety of the P140005 HA included 229 subjects (116 P140005 HA, 113 P980044 HA). In the P980044 HA group, 26 subjects (23.0%) experienced adverse events (AEs). In this group, 6 events (5.3%) were judged as possibly related to the device (4 cases of local pain

⁴ Summary of Safety and Effectiveness Data (SSED)-Visco-3. https://www.accessdata.fda.gov/cdrh_docs/pdf/P980044S027B.pdf

and 2 cases of swelling). In the P140005 HA group, 21 subjects (18.1%) experienced AEs. In this group 2 events (1.7%) were judged possibly related to the device (1 case of local pain and 1 case of rash). One serious adverse event (SAE) that was unrelated to the device, prostatic hyperplasia treated with surgical excision, was reported in the P980044 HA group. There were no statistically significant differences in the incidence rates of these adverse events between the P140005 HA and P980044 HA groups. A summary of AEs is provided in Table 3.

Table 3: Adverse events reported in Yong Ping study

	Category	P980044 HAGroup/N(%)	P140005 HAGroup/ N(%)	Statistics	P value	Method
AE	Yes	26 (23.0)	21 (18.1)	0.844	0.358	Chi-square
	No	87 (77.0)	95 (81.9)			
	Total	113	116			
Related AE	Yes	6 (5.3)	2 (1.7)	--	0.167	Fisher
	No	107 (94.7)	114 (98.3)			
	Total	113	116			
SAE	Yes	1 (0.9)	0 (0.0)	--	1.000	Fisher
	No	112 (99.1)	116 (100.0)			
	Total	113	116			

Note: AEs that were definitely related, probably related, and possibly related to the device and abnormal laboratory findings were judged as Related AEs.

In addition, TriVisc has been commercially distributed in 40 countries outside of the United States. TriVisc is also approved in 23 other countries but not presently distributed. TriVisc (sold ex-U.S. as Adant) has been on the market in Japan since 1995 and in Europe since 1996. From the time of its first marketing through 2012 over 35 million syringes were distributed with no major safety concerns related to the product.

CLINICAL STUDIES

The primary clinical performance testing to demonstrate effectiveness of TriVisc, as per the application of Section 216 of the Food and Drug Administration Modernization Act (1997), is obtained from the Summary of Safety and Effectiveness Data (SSED) for a viscosupplement approved under Premarket Application (PMA) supplement P980044/S27.

A clinical study was performed to establish a reasonable assurance of safety and effectiveness of three weekly intra-articular injections of the viscosupplement approved under P980044/S27 for the treatment of pain due to OA of the knee in patients who had failed to respond adequately to conservative non-pharmacologic therapy and simple analgesics. The study was performed in the United States (US) under IDE (Investigational Exempt Device) G130271. Data from this clinical study were the basis for the approval decision of this viscosupplement under P980044/S27.

Study Design

The study was a pivotal, prospective, multi-center, randomized, double-blind, parallel arm, active controlled, and non-inferiority clinical study. The active comparator arm was a commercially available hyaluronan, a legally marketed alternative with identical indications for use.

The primary objective of the study was to demonstrate non-inferiority of the treatment group for the viscosupplement approved under P980044/S27 to the active control group for the relief of knee joint pain in subjects with OA of the knee as measured by the Western Ontario and McMaster Universities Osteoarthritis Index Visual Analog Scale (WOMAC VAS) (0-100 mm) pain subscale score change from baseline (CFB) over Week 3, Week 6, and Week 12 in the per-protocol set, using mixed model repeated measures (MMRM). The non-inferiority margin was 8% (-8 mm). The statistical test to conclude non-inferiority required the lower bound of the 2-sided 95% confidence interval (CI) of the viscosupplement approved under P980044/S27 minus the commercially available hyaluronan CFB least square means be greater than -8 mm. The control group was the commercially available hyaluronan.

All subjects diagnosed with OA of the knee who met all inclusion criteria and no exclusion criteria, and who provided written informed consent, were recruited for enrollment into the study. Eligible subjects were randomly assigned in a 1:1 ratio to receive either the viscosupplement approved under P980044/S27 or the active control.

The analysis of effectiveness was based on the 384 evaluable patients over the 12-week time point. Key effectiveness outcomes are presented in

Table Table 3 below. No secondary endpoints for effectiveness were proposed.

Mean baselines of WOMAC VAS pain subscale were 57.83 mm (standard deviation [SD]: 9.654) in the viscosupplement approved under P980044/S27 group and 58.40 mm (SD: 8.977) in the active control group. The least squares mean for CFB for viscosupplement approved under P980044/S27 minus that of the active control over Week 3, Week 6, and Week 12 for WOMAC VAS pain subscale score was -3.30 mm and the 95% CI lower bound of this difference was -6.77 mm. The lower bound -6.77 mm was greater than -8 mm, leading to the conclusion that viscosupplement approved under P980044/S27 is non-inferior to the active control.

Results at the end of the study (i.e., at Week 12) yielded an average 52.5% reduction in pain for those patients treated with viscosupplement approved under P980044/S27 (based on a mean CFB of 30.48 mm and mean baseline pain of 57.83 mm).

Table 4: Key Effectiveness Parameters

Average over Weeks 3, 6 and 12	P010029⁵ HA (Active Control) (N=189)	P980044/S27 (N=195)	CFB Difference
Baseline WOMAC VAS Pain (mm) (Mean [SD])	58.40 (8.977)	57.83 (9.654)	
LS Mean (standard error [SE])	30.15 (1.303)	26.85 (1.270)	-3.30 (1.762)

⁵ Summary of Safety and Effectiveness Data (SSED)- P010029 Euflexxa
https://www.accessdata.fda.gov/cdrh_docs/pdf/P010029S008b.pdf

of Change from Baseline			
95% CI	27.59 – 32.71	24.35 – 29.35	-6.77 – 0.17

*FDA approved three-injection HA product

A comparative clinical trial of the viscosupplement approved under P980044/S27 to a commercially available hyaluronan successfully demonstrated non-inferiority within an 8% margin as determined by comparisons of the change from baseline (CFB) of WOMAC VAS pain subscale scores over the 12-week duration of the trial. The least squares mean for CFB for the viscosupplement approved under P980044/S27 minus that of the P010029 HA (active control) over Week 3, Week 6, and Week 12 for the WOMAC VAS pain subscale score was -3.30 mm and the 95% CI lower bound of this difference was -6.77 mm and thus was greater than the -8 mm margin required to demonstrate non-inferiority.

Supplemental Supportive Clinical Data

Although not utilized in the primary effectiveness evaluation, additional data supporting the effectiveness was provided. In a total of 137 patients in 3 separate studies^{6,7,8} the three-injection regimen of TriVisc was compared to three different FDA approved intra-articular hyaluronans.

⁶ Dıraçođlu, D. et al. *J Back and Musculo Rehab.* 2016;16: 53. Single versus multiple dose hyaluronic acid: Comparison of the results.

⁷ Özgönel, L. et al. *Istanbul Tıp Dergisi* 2008;1: 53-57. Comparison of different hyaluronates.

⁸ Ulucay, I. et al. *Acta Orthop Traumatol Turc* 2007;41: 337-342. The use of arthroscopic debridement and viscosupplementation in knee osteoarthritis.

DETAILED DEVICE DESCRIPTION

Each 3mL prefilled syringe of TriVisc contains:

Sodium Hyaluronate	25.0mg
Sodium Chloride	21.3mg
Disodium Phosphate Dodecahydrate	1.5mg
Sodium Hydroxide	q.s. to adjust pH
Hydrochloric acid	q.s. to adjust pH
Water for Injection	q.s. 2.5mL

HOW SUPPLIED

TriVisc is supplied as a sterile, non-pyrogenic solution in 3mL pre-filled syringe.

DIRECTIONS FOR USE

TriVisc is administered by intra-articular injection. A treatment cycle consists of three injections given at weekly intervals. Injection of subcutaneous lidocaine or similar local anesthetic may be recommended prior to injection of TriVisc.

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

Precaution: Do not use TriVisc if the package is opened or damaged. Store in the original packaging (protected from light) below 86°F (30°C). DO NOT FREEZE. Do not use after expiration date indicated on package. The shelf life is 42 months.

Precaution: Strict aseptic administration technique must be followed.

Precaution: Remove joint effusion, if present, before injection TriVisc.

Take care to remove the tip cap of the syringe and needle aseptically. Inject TriVisc into the joint through a 21-23 gauge needle.

Inject the full 2.5mL in one knee only. If treatment is bilateral, a separate syringe should be used for each knee.

Precaution: The prefilled syringe is intended for single use. The content of the syringe must be used immediately once the container has been opened. Discard any unused TriVisc.

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