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 AMELIA[1] and Yong Ping[2] studies, used to establish reasonable assurance of the safety of established in the approval of another intra-articular hyaluronan (HA) under P140005[3] (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 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 (2), 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	2
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 P980044[4] 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 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 HA Group/ N(%)	P140005 HA Group/ 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.

TriVisc®

(sodium hyaluronate)

Patient Information

Product Information

TriVisc® (sodium hyaluronate)

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 TriVisc. If you do not understand this information or want to know more, ask your doctor.

Glossary of Terms

Hyaluronate: Hyaluronate is a natural substance found in the human body and is present in very high amounts in joints. The body's own hyaluronate 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, such as aspirin, naproxen, ibuprofen, and Celebrex, for reducing pain, fever and inflammation.

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

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For more Information, please refer to the Full Prescribing Information for TriVisc.

General

WHAT IS TRIVISC (SODIUM HYALURONATE)?

TriVisc is a product from the class of products known as hyaluronic acid, sodium hyaluronate, or hyaluronan (HA), and also known as viscosupplementation therapy. It helps supplement the viscous properties of the fluid in your knee joint. It is approved for treatment of pain due to osteoarthritis of the knee in patients who do not get adequate relief from simple painkillers like acetaminophen or from exercise and physical therapy.

WHAT IS TRIVISC USED FOR?

TriVisc is used to relieve knee pain due to OA. It is given to patients who do not get enough relief from simple pain medications, such as acetaminophen, or from exercise and physical therapy.

HOW IS TRIVISC GIVEN?

TriVisc is administered by intra-articular injection. Intra-articular means your healthcare professional will insert a needle into the space in your knee joint that contains fluid used for lubrication and cushioning.

HOW DOES TRIVISC WORK?

The precise mechanism by which TriVisc works is unknown. The fluid (synovial fluid) in your knee helps to lubricate and cushion the joint during movement. The major component in the synovial fluid is hyaluronic acid, the same active component of TriVisc. One of the early effects of OA is to break down this fluid, making it less effective. It is thought that TriVisc injection helps restore the synovial fluid to a healthier state, thereby reducing the pain of OA.

ARE THERE ANY REASONS WHY I SHOULD NOT RECEIVE TRIVISC?

Your doctor will determine if you are a candidate for TriVisc treatment, but you should also be aware that TriVisc should not be administered to patients who:

- have ever had an allergic response to hyaluronate-containing products such as a rash, itching, hives, flushing, swelling of the face, tongue or throat, and/or difficulty breathing;
- have a knee joint infection or skin disease, or infection around the area where the injection will be given, or circulatory problems in the legs.

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:

- TriVisc is only for injection into the knee, performed by a qualified healthcare professional.
- TriVisc 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 hyaluronate products.
- 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 effectiveness of repeat treatment cycles of TriVisc has not been established.
- Use of TriVisc in joints other than the knee and for conditions other than OA has not been tested.
- TriVisc 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.
- TriVisc has not been tested in children (21 years of age or younger).

WHAT ARE THE POSSIBLE SIDE EFFECTS?

- Some side effects (also called reactions) may occur during the use of TriVisc with symptoms such as knee pain, inflammation, reddening, swelling appearing at the injection site, joint pain. If any of these symptoms or signs appears after you are given TriVisc or if you have any other problems, you should call your doctor.
- Because TriVisc is administered through a needle you may experience some local pain or discomfort when it is administered, as may be expected with all injections.

WHAT ARE THE POTENTIAL BENEFITS OF TRIVISC?

A clinical study was conducted for a viscosupplement approved under Premarket Application (PMA) supplement P980044/S27 that is very similar to TriVisc. The study was performed in the United States (US) and the viscosupplement approved under P980044/S27 was compared to another U.S. commercially available hyaluronan, a legally marketed alternative with identical indications for use. The analysis of effectiveness was based on the 384 patients followed over the 12-week time point. 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 the viscosupplement approved under P980044/S27 (based on a mean change from baseline (CFB) of 30.48 mm and mean baseline pain of 57.83 mm). The study successfully demonstrated non-inferiority within an 8% margin as determined by comparisons of the 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 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

WHAT ADVERSE EVENTS WERE OBSERVED IN THE CLINICAL STUDIES?

The primary clinical performance testing to assess the safety of TriVisc were based on two clinical studies, the AMELIA and Yong Ping studies, used to establish reasonable assurance of the safety of a similar viscosupplement approved under P140005. TriVisc is of identical chemical formulation to this other approved viscosupplement and differs only in that less of the device is injected (3 weekly injections of 2.5 ml for TriVisc and 5 weekly injections of the approved viscosupplement). Thus, the clinical studies used to provide evidence of the reasonable assurance of the safety under the data original submitted for approval of this viscosupplement (P14005) are directly applicable to TriVisc as well.

The primary evidence of the safety of the identical viscosupplement was provided by the comparison of the viscosupplement to PBS (saline) in a study called AMELIA. In this study, four cycles of 5 injections of the viscosupplement 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 viscosupplement included 306 subjects (153 viscosupplement, 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 viscosupplement 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 (2), and arthritis (1).

Table 1: Related adverse events by severity

Related Adverse Events	Viscosupplement (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	2
Arthritis	--	--	--	--	1	1
Heaviness	1	--	1	--	--	--
Total	7	8	15	12	2	14

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 4 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	P010029[5] 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]) of Change from Baseline	30.15 (1.303)	26.85 (1.270)	-3.30 (1.762)
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.

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.

To ensure a tight seal and prevent leakage during administration, firmly HOLD the luer lock when removing the tip cap and attaching the needle. Take care not to rotate the luer lock which can lead to loosening of the hub. Inject TriVisc into the knee 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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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
4 Summary of Safety and Effectiveness Data (SSED)-Visco-3. https://www.accessdata.fda.gov/cdrh_docs/pdf/P980044S027B.pdf
5 Summary of Safety and Effectiveness Data (SSED)- P010029 Euflexxa https://www.accessdata.fda.gov/cdrh_docs/pdf/P010029S008b.pdf
6 Dıraçöglu, D. et al. J Back and Musculo Rehab. 2016;16: 53. Single versus multiple dose hyaluronic acid: Comparison of the results.
7 Özgönenel, 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.

Supporting evidence of safety is provided by the comparison of the viscosupplement to a previously approved viscosupplement under P980044 in the Yong Ping study for time periods up to 6 weeks. The population of patients evaluated to assess the safety of the viscosupplement equivalent to TriVisc included 229 subjects (116 TriVisc equivalent , 113 previously approved viscosupplement). In the previously approved viscosupplement X 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 and 2 cases of swelling). In the TriVisc equivalent 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 previously approved viscosupplement group. There were no statistically significant differences in the incidence rates of these adverse events between the TriVisc equivalent and the previously approved viscosupplement groups. A summary of AEs is provided in Table 2.

Table 2: Adverse events reported in Yong Ping study

	Category	Previously Approved Viscosupplement Group/N(%)	TriVisc Equivalent Viscosupplement Group/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.

Overall, these results indicated that the viscosupplement equivalent to TriVisc, and therefore TriVisc, is safe and well tolerated.

Specific to products with the same formulation as TriVisc, the possible adverse reactions that have been reported in the literature and collected as post-marketing experience worldwide include: injection site reactions (pain/ swelling/ effusion/ redness/ warmth); itching; swelling of the face, eyelids, mouth and/or extremities; rash; hives; redness in face; nausea; vomiting; and fever.

WHAT OTHER TREATMENTS ARE AVAILABLE FOR OA?
If you have OA, there are other things you can do besides getting TriVisc. These include:

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

Drug therapy
- Pain relievers such as acetaminophen and narcotics
- Drugs that reduce inflammation and pain (signs of inflammation are swelling, pain or redness), such as aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen, naproxen and Celebrex
- Steroids injected directly into your knee

THINGS YOU SHOULD KNOW ABOUT TRIVISC.
- TriVisc is only for injection into the knee, performed by a doctor or other qualified health care professional.
- If you have pain in both knees, the effects of pain relief on the knee opposite to the one injected have not been evaluated. Your doctor may recommend that both knees be injected.
- After you receive the injection, you may need to avoid strenuous activities such as jogging, tennis, heavy lifting, or standing for a long time for approximately 48 hours.
- If any of the above symptoms or signs appear after you are given TriVisc, or if you have any other problems, you should call your doctor.

WHY IS MY DOCTOR RECOMMENDING I RECEIVE TRIVISC?
TriVisc is indicated for patients with osteoarthritis knee pain who do not obtain adequate relief from simple painkillers, like acetaminophen (R) superscript, or from exercise and physical therapy. Ask your doctor for additional information and discuss your treatment options.

IS TRIVISC APPROVED FOR USE IN THE U.S.?
TriVisc was approved for use in the United States in November 2017. TriVisc has demonstrated a very favorable safety profile, with over 35 million doses administered worldwide since its first approval, and has been studied in over 30 clinical trials for use in relieving osteoarthritis knee pain.

WHAT IS TRIVISC MADE FROM?
Hyaluronic acid is a natural chemical found in almost all species and various parts of your body. It is in high amounts particularly in joint tissues and in the fluid that fills the knee joint space (synovial fluid). TriVisc is made from an extraction and purification of hyaluronic acid from fermentation of bacteria that make hyaluronic acid identical in chemical composition to human hyaluronic acid.

WILL MY INSURANCE COVER TRIVISC?
Most insurance carriers and Medicare cover TriVisc. The process of obtaining reimbursement varies from plan to plan so talk with your doctor's office and your insurance provider before you begin treatment to find out if TriVisc is covered.

Treatment

ARE THREE INJECTIONS REQUIRED?
Clinical investigations with TriVisc have demonstrated that three injections one week apart provide optimal pain relief. The effectiveness of less than three injections has not been evaluated. You should discuss this with your doctor. Completion of the full injection treatment course is recommended to achieve the greatest therapeutic benefit.

HOW DO I KNOW IF TRIVISC IS RIGHT FOR ME?
A doctor is the best person to advise you on any course of treatment. TriVisc is approved for the treatment of pain due to osteoarthritis of the knee in patients who do not get adequate relief from simple painkillers or from exercise and physical therapy.

AM I TOO OLD FOR TRIVISC INJECTIONS?
There are no specific precautions or contraindications regarding the use of TriVisc in older patients.

CAN I TAKE OTHER MEDICATIONS WITH TRIVISC?
Because TriVisc is injected directly into the joint rather than administered systemically and there are no known drug interactions, you may be able to take other medications with it. It is not known to interfere with other pain relievers and anti-inflammatory drugs. The safety and effectiveness of the use of TriVisc at the same time as other intra-articular injections, such as steroids, have not been established. Because it is administered locally it is unlikely that you will observe any benefit in joints not specifically injected. You should discuss all of your current medications and vitamin supplements with your physician on a periodic basis.

CAN I RECEIVE TRIVISC IN BOTH OF MY KNEES?
Yes, if both knees have pain. TriVisc treatment may be given in both knees simultaneously or separately, according to your physician's recommendations. Because TriVisc is only injected locally into the knee joint and not administered systemically, it is not likely that injections into one knee will have an effect on the opposite knee if it is not injected. In addition, it is unknown whether a good response in one knee is a good predictor of an equivalent response in the opposite knee should you decide to have this therapy.

SHOULD I MODIFY MY LEVEL OF PHYSICAL ACTIVITY AFTER RECEIVING TRIVISC TREATMENT?
It is recommended that you avoid strenuous activities such as jogging, tennis, and heavy lifting for at least 48 hours after receiving an injection. Your doctor will advise you about the level of activity that is right for you, but in general, patients are able to maintain their normal daily activities after receiving TriVisc treatment.

CAN TRIVISC BE USED IN JOINTS OTHER THAN THE KNEE?
The U.S. Food and Drug Administration has only approved TriVisc for use in the treatment of OA of the knee. The FDA has not approved or made an evaluation regarding the safety and effectiveness in other joints.

IS TRIVISC A CURE FOR OSTEOARTHRITIS OF THE KNEE?
There is no cure for osteoarthritis. TriVisc is a treatment for the symptoms of knee pain of osteoarthritis.

Benefits

WHEN CAN I EXPECT TO EXPERIENCE PAIN RELIEF?
Each patient's response to TriVisc may vary, depending on severity of your OA, degree of pain, and pre-existing medical conditions. In some patients, successful treatment may reduce pain within the first week after treatment begins. However, based upon clinical trials, most patients experienced pain relief after their third injection of TriVisc.

IS TRIVISC TREATMENT EFFECTIVE IN KNEES WITH ADVANCED OSTEOARTHRITIS AND LOSS OF CARTILAGE?
Most of the clinical studies with TriVisc have selected patients with mild to moderate OA.

WHAT ARE THE BENEFITS OF RECEIVING TRIVISC TREATMENT?
Successful treatment with TriVisc should reduce pain in an osteoarthritic knee. Because it is a local treatment, TriVisc should not interfere with any medicine that the patient may take.

HOW LONG CAN I EXPECT THE BENEFIT OF TRIVISC TO LAST?
Each patient reacts differently to TriVisc treatment. Three injections given at weekly intervals can provide most patients up to 12 weeks of pain relief. The duration of pain relief you experience may vary.

Safety

HOW SAFE IS TRIVISC?
Extensive safety and toxicity tests were performed on TriVisc. Viscosupplements equivalent to TriVisc are approved in over 60 countries worldwide. These viscosupplements have been in use since 1995 in Japan, 1996 in Europe, and 2015 in the U.S., with over 4 million injections given worldwide. In clinical trials, transient local pain or swelling occurred with some patients with injections of TriVisc. Since introduction into the global market, TriVisc has not been withdrawn in any market because of safety concerns.

For more Information, please ask your doctor or refer to the Full Prescribing Information for TriVisc.