VISCO-3™

(sodium hyaluronate)

CAUTION

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

DESCRIPTION

VISCO-3™ is a sterile, viscoelastic non-pyrogenic solution of purified, high molecular weight (620,000-1,170,000 daltons) sodium hyaluronate (hyaluronan) having a pH of 6.8-7.8. Each one mL of VISCO-3™ contains 10 mg of sodium hyaluronate (hyaluronan) dissolved in a physiological saline (1.0% solution). The sodium hyaluronate (hyaluronan) is extracted from chicken combs. Sodium hyaluronate (hyaluronan) is a polysaccharide containing repeating disaccharide units of glucuronic acid and N-acetylglucosamine.

INDICATIONS AND USAGE

VISCO-3™ 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

General

・The effectiveness of a single treatment cycle of less than 3 injections has not been established.

・Strict aseptic administration technique must be followed.

・Remove joint effusion, if present, before injecting VISCO-3™.

・Transient increases in inflammation following any intra-articular hyaluronan injection have been reported in some patients with inflammatory joint conditions.

・The safety and effectiveness of the use of VISCO-3™ in joints other than the knee have not been established.

・The safety and effectiveness of the use of VISCO-3™ concomitantly with other intra-articular injectables have not been established.

・Use caution when injecting VISCO-3™ into patients who are allergic to avian proteins, feathers and egg products.

・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 VISCO-3™.

・Do not use VISCO-3™ if the package is opened or damaged. Store in the original packaging below 77°F (25°C). DO NOT FREEZE. Do not use after expiration

date indicated on package. Shelf life is 42 months.

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 VISCO-3^{TM}.
- 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.
- The effectiveness of repeat treatment cycles of VISCO-3^{TM} has not been established.

Use in Specific Populations

- Pregnancy: The safety and effectiveness of VISCO-3^{TM} have not been established in pregnant women.
- Nursing Mothers: It is not known if VISCO-3^{TM} is excreted in human milk. Excretion has been seen in rat milk. The safety and effectiveness of VISCO-3^{TM} have not been established in lactating women.
- Pediatrics: The safety and effectiveness of VISCO-3^{TM} have not been demonstrated in pediatric patients (i.e., patients 21 years or younger).

ADVERSE EVENTS

Adverse events (AEs) in the multicenter clinical trial were reported in 51% (107/209) of subjects in the VISCO-3^{TM} group and 52% (109/211) of subjects in the commercially available hyaluronan (active control) group. Those occurring in >5% of subjects are noted in Table 3. Study device related AEs were reported in 4% (9/209) of subjects in the VISCO-3^{TM} group and 7% (14/211) of subjects in the active control group. The most frequently reported device-related AEs in the VISCO-3^{TM} group were arthralgia (1%), joint swelling (1.4%), and injection site pain (1.0%). See Table 4. There was one subject in the active control group who died; the AE was not related to the study device. There were 7 subjects who each experienced one serious adverse event; none were considered related to the study device in either group. Overall, these results indicate that VISCO-3^{TM} is safe and well tolerated.

Post-market experience

The possible adverse reactions that have been reported in the literature and collected as post-marketing experience worldwide for the SUPARTZ formulation (same as VISCO-3) include:

- Injection site reactions (pain/ swelling/ effusion/ redness/ warmth). Rare cases of severe reactions have been reported.
- Other adverse reactions include: Itching; swelling of the face, eyelids, mouth and/or extremities; rash; hives; redness in face; nausea; vomiting and fever. Anaphylactic/anaphylactoid reactions accompanied by transient hypotension (sudden drop in blood pressure), have been rarely reported, all of which resolved either spontaneously or after conservative treatment.

Literature has also shown that repeated treatment cycles of the SUPARTZ formulation contain no evidence of an increased safety risk. The frequency and severity of adverse events occurring during repeat treatment cycles did not increase over that reported for a single treatment cycle.

Potential adverse events

Below is a comprehensive list of the potential adverse events (e.g., complications) generally associated with intra-articular hyaluronan injections for the treatment of pain in osteoarthritis of the knee.

- Aggravated osteoarthritis

· Arthralgia (knee pain)
· Arthropathy
· Arthrosis
· Baker's cyst
· Bursitis
· Chills
· Dizziness
· Headache
· Hives
· Immune response
· Infection
· Injection site reaction (edema/ erythema/ pain)
· Joint (knee) disorder (effusion/ stiffness/ swelling)
· Localized osteoarthritis
· Malaise
· Muscle cramps
· Nausea
· Pain in limb
· Paresthesia
· Peripheral edema
· Phlebitis
· Pruritus
· Rash
· Tendonitis

CLINICAL STUDY

Study Design

The safety and effectiveness of VISCO-3™ was studied in a pivotal, 12-week, multi-center, randomized, double-blind, parallel arm, active controlled (i.e., commercially available hyaluronan), non-inferiority study in the US. Eligible subjects were randomly assigned in a 1:1 ratio to receive either VISCO-3™ or the active control and received 3 injections administered once a week (1 week apart).

Measures of Effectiveness

The primary objective of the study was to demonstrate non-inferiority of VISCO-3™ group 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 (WOMAC) visual analog scale (VAS) (0-100 mm) pain subscale score change from baseline (CFB) over Week 3, Week 6, and Week 12 in the per-protocol set. 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) around the VISCO-3™ minus the commercially available hyaluronan change from

baseline CFB least square means to be greater than −8 mm.

Clinical Trial Results

Patient Population and Demographics

A total of 420 subjects received at least one injection of either VISCO-3™ or the active control. The safety set (SS) included 209 VISCO-3™ subjects and 211 active control subjects. Subject disposition and demographic data are shown in Table 1.

All safety analyses were performed on SS which included all subjects who received at least one injection. The SS included 209 subjects in the VISCO-3™ group and 211 subjects in the active control group. Primary effectiveness was analyzed in the per-protocol set (PPS) which included all randomized subjects who had at least 1 post-baseline WOMAC VAS pain subscale score except those with important protocol deviations. The PPS was composed of 195 subjects in the VISCO-3™ group and 189 subjects in the active control group.

Table 1: Demographic Data (Safety set)

Demographic or Baseline Characteristic	**Active Control (N=211) n (%)**	**VISCO-3™ (N=209) n (%)**
Age (years)		
n	211	209
Mean (SD)	60.9 (9.33)	59.3 (9.30)
Min-Max	42-80	40-79
Sex (n [%])		
Male	76 (36.0)	71 (34.0)
Female	135 (64.0)	138 (66.0)
Ethnicity (n [%])		
Hispanic or Latino	16 (7.6)	16 (7.7)
Not Hispanic or Latino	195 (92.4)	193 (92.3)
Race (n [%])*		
American Indian or Alaskan Native	0	4 (1.9)
Asian	8 (3.8)	6 (2.9)
Black or African American	41 (19.4)	47 (22.5)
Native Hawaiian or Other Pacific Islander	2 (0.9)	1 (0.5)
White	160 (75.8)	156 (74.6)
Body Mass Index		
n	207	207
Mean (SD)	32.35 (7.174)	33.13 (7.574)
Min – Max	19.9-56.8	15.2-55.0
Baseline WOMAC VAS Pain (mm) (Mean [SD])	58.40 (8.977)	57.83 (9.654)

*A subject could mark more than one race.

Safety Results

The analysis of safety was based on the cohort of 420 subjects that received at least one out of the total of three injections during the period of 12 weeks of evaluation. The key safety outcomes for this study are presented below in Tables 2-4. Device-related adverse events (AEs) are reported in Table 4.

Adverse events that occurred in the PMA clinical study:

Adverse events were reported in 51% (107/209) of subjects in the VISCO-3™ group and 52% (109/211) of subjects in the active control group, as summarized below in Table 2. Study device-related AEs were reported in 4% (9/209) of subjects in the VISCO-3™ group and 7% (14/211) of subjects in the active control group. There was one subject in the active control group who died; the AE was not related to the study device. There were 7 subjects who each experienced one serious adverse event (SAE); none were considered related to the study device.

No clinically relevant changes were seen in vital signs or physical examinations.

Table 2: Overall Summary of Treatment-Emergent Adverse Events (TEAEs)

Category	Active Control (N=211) n (%)	VISCO-3™ (N=209) n (%)
Subjects with ≥1 TEAE	109 (51.7)	107 (51.2)
Subjects with ≥1 TEAE related to study device	14 (6.6)	9 (4.3)
Subjects with ≥1 serious adverse event (SAE)	6 (2.8)	1 (0.5)

Treatment-Emergent Adverse Events (TEAEs) occurring in >5% of subjects are summarized below in Table 3 according to numbers and percentages of subjects who experienced one or more TEAEs in each treatment group.

Table 3: TEAEs by System Organ Class and Preferred Term Occurring in >5% of Subjects in Either Treatment Group (Active Control or VISCO-3™)

System Organ Class Preferred Term	Active Control (N=211) n (%)	VISCO-3™ (N=209) n (%)
Musculoskeletal and connective tissue disorders	61 (28.9)	54 (25.8)
Arthralgia	24 (11.4)	23 (11.0)
Back pain	10 (4.7)	15 (7.2)
Nervous system disorders	31 (14.7)	25 (12.0)
Headache	25 (11.8)	22 (10.5)

Note: Subjects with multiple events in the same category are counted only once in that category; subjects with events in multiple categories are counted once in each category.

TEAEs considered to be related to the study device are summarized below in Table 4 according to numbers and percentages of subjects who experienced one or more device-related TEAEs in each treatment group. The most frequently reported specific device-related AEs in the VISCO-3™ group were arthralgia (1%), joint swelling (1.4%),

and injection site pain (1.0%).

Table 4: Subjects with Device-Related AE by System Organ Class and Preferred Term

System Organ Class Preferred Term	Active Control (N=211) n (%)	VISCO-3™ (N=209) n (%)
Musculoskeletal and connective tissue disorders	8 (3.8)	6 (2.9)
Joint swelling	3 (1.4)	3 (1.4)
Arthralgia	5 (2.4)	2 (1.0)
Joint instability	1 (0.5)	1 (0.5)
Joint stiffness	1 (0.5)	1 (0.5)
General disorders and administration site conditions	5 (2.4)	3 (1.4)
Injection site pain	0	2 (1.0)
Edema peripheral	2 (0.9)	1 (0.5)
Injection site erythema	1 (0.5)	0
Injection site rash	1 (0.5)	0
Pain	1 (0.5)	0
Nervous system disorders	3 (1.4)	2 (1.0)
Headache	2 (0.9)	1 (0.5)
Neuralgia	0	1 (0.5)
Hemiparesis	1 (0.5)	0
Skin and subcutaneous tissue disorders	1 (0.5)	0
Pruritus	1 (0.5)	0

Note: Subjects with multiple events in the same category are counted only once in that category; subjects with events in multiple categories are counted once in each category.

Safety Conclusions

The risks of the device are based on data collected in a clinical study conducted to support approval of the PMA supplement as described above. Safety data indicated comparable safety and tolerability of VISCO-3™ to the active control. Of these AEs, less than 10% were considered related to the study device in either group. None of the SAEs were considered related to the study device in either group. No clinically relevant changes were observed in vital signs or physical examinations. Overall, these results indicated that VISCO-3™ is safe and well tolerated.

Effectiveness Results

Mean baselines of WOMAC VAS pain subscale in VISCO-3™ and the active control were 57.83 mm (standard deviation [SD]: 9.654) and 58.40 mm (SD: 8.977), respectively. The least squares mean for CFB for VISCO-3™ 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 VISCO-3™ is non-inferior to the active control (Table 5).

Table 5: Primary Effectiveness Analysis: CFB on the 100 mm WOMAC VAS Pain Subscale Score over Week 3, Week 6, and Week 12 (Per-Protocol Set)

Average over Weeks 3, 6, and 12	Active Control (N=189)	VISCO-3™ (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

Effectiveness Conclusions

A comparative clinical trial of VISCO-3™ 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 VISCO-3™ 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.

DETAILED DEVICE DESCRIPTION

Each 2.5 mL prefilled syringe of VISCO-3™ contains:

Sodium Hyaluronate (hyaluronan)	25.0 mg
Sodium Chloride	21.25 mg
Dibasic Sodium Phosphate Dodecahydrate	1.343 mg
Sodium Dihydrogen Phosphate Dihydrate	0.04 mg
Water for Injection	q.s.

HOW SUPPLIED

VISCO-3™ is supplied as a sterile, non-pyrogenic solution in 2.5 mL prefilled syringe.

DIRECTIONS FOR USE

VISCO-3™ is administered by intra-articular injection once a week (1 week apart) for a total of 3 injections. Injection of subcutaneous lidocaine or similar local anesthetic may be recommended prior to injection of VISCO-3™.

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 VISCO-3™ if the package is opened or damaged. Store in the original packaging below 77°F (25°C). DO NOT FREEZE. Do not use after expiration date indicated on package. Shelf life is 42 months.

Precaution: Strict aseptic administration technique must be followed.

Precaution: Remove joint effusion, if present, before injection of VISCO-3™.

Take care to remove the tip cap of the syringe and needle aseptically. Inject VISCO-3™ into the joint through a 22-23 gauge needle.

Inject the full 2.5 mL 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 VISCO-3™.

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