INFORMATION FOR PRESCRIBERS

Cingal® Hyaluronic Acid plus Triamcinolone Hexacetonide, Intra-articular

CAUTION:

This product is available under medical recommendation and the administration must be performed by a physician.

DESCRIPTION:

Cingal® is a sterile, non-pyrogenic suspension of micronized steroid particles in a viscoelastic hyaluronic acid (HA) gel contained in a single-use syringe. Cingal® is a modification of the Health Canada-approved viscosupplement, Monovisc® (License number 80474). The HA used in Cingal® and Monovisc® is derived from bacterial cells and is cross-linked with a proprietary cross-linker. The steroid used in Cingal® is triamcinolone hexacetonide (TH), a water-insoluble corticosteroid.

INDICATIONS:

Cingal® 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 to simple analgesics (e.g., acetaminophen). Cingal® includes an ancillary steroid to provide additional short-term pain relief.

CONTRAINDICATIONS:

- Do not administer to patients with known hypersensitivity (allergy) to hyaluronate preparations
- Do not administer to patients with known hypersensitivity (allergy) to triamcinolone hexacetonide preparations.
- Do not administer to patients with known sensitivity to any of the materials contained in Cingal®.
- Do not administer to pregnant women, or women who suspect they might be pregnant; as the safety of Cingal® in pregnant women has not been tested.
- Do not inject Cingal® in the knees of patients with infections or skin diseases in the area of the injection site or joint.

WARNINGS:

- Do not concomitantly use disinfectants containing quaternary ammonium salts for skin preparation as hyaluronan can precipitate in their presence.
- Transient increases in inflammation in the injected knee following intra-articular injection have been reported in some patients with inflammatory osteoarthritis.

PRECAUTIONS:

- Cingal® should be used with great caution in patients with impaired cardio-renal function, endocrine, or other diseases or conditions that use of corticosteroid is warned.
- Strict aseptic injection technique should be used during the application of Cingal®.
- The safety and effectiveness of the use of Cingal® in joints other than the knee have not been demonstrated.
- The effectiveness of Cingal® has not been established for more than one course of treatment.
- STERILE CONTENTS. The pre-filled syringe is intended for single use only. The contents of the syringe should be used immediately after opening. Discard any unused Cingal® Do not resterilize.
- Do not use Cingal® if the package has been opened or damaged.
- Store Cingal® in its original package at room temperature (below 77°F/25°C). DO NOT FREEZE.
- Remove joint effusion, if present, before injecting Cingal®.
- Only medical professionals trained in accepted injection techniques for delivering agents into the knee joint should inject Cingal® for the indicated use.

Information for Patients

- Transient pain or swelling may occur after the intra-articular (IA) injection.
- As with any invasive joint procedure, it is recommended that patients avoid strenuous or prolonged (i.e., more than one hour) weight-bearing activities such as running or tennis within 48 hours following the intra-articular injection.

Use in Specific Populations

- **Pregnancy:** The safety and effectiveness of the use of Cingal® in pregnant women has not been tested.
- **Nursing Mothers:** It is not known if Cingal® 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 Cingal® in pediatric patients (≤ 21 years of age) has not been tested.

POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH:

Reported Device-related Adverse Events

Potential adverse effects, including complications associated with intra-articular hyaluronic injections and intra-articular corticosteroid injections, include arthralgia; local swelling, effusion, or stiffness of the knee; arthropathy; injection site pain, edema, erythema or reaction; facial flushing, post-injection flare, injection site skin atrophy, calcification, or hypopigmentation. Diabetics may observe a transient increase in blood sugar. Rare side effects include infection, tendinopathy, or Nicolau's syndrome (dermatitis).

A complete listing of the frequency and rate of adverse events identified in the Cingal® clinical study is provided in the Safety section.

CLINICAL STUDY

Cingal 13-01 Pivotal Clinical Trial

Study Design:

Cingal 13-01 was a randomized, double-blinded, saline-controlled (with an active comparator arm) study conducted at 27 centers in Canada and Europe to evaluate the safety and effectiveness of a single injection of Cingal® in patients with symptomatic osteoarthritis of the knee. A total of 368 patients were enrolled. Patients were randomized in a 2:2:1 ratio to Cingal®, Monovisc®, or saline injection. The outcome measures collected included the WOMAC Pain, Stiffness, Physical Function, and Total Scores; OMERACT-OARSI Responder Index; and Investigator and Patient Global Assessments. The primary endpoint was the change from baseline in knee pain as measured by the WOMAC Pain Score (100 mm VAS) through 12 weeks post treatment comparing the Cingal® group to the saline control group.

Study Population:

The patients enrolled in the study were between 40 and 75 years old and had the diagnosis of idiopathic OA based upon clinical and/or radiographic criteria of the American College of Rheumatology. 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 368 patients were randomized to either Cingal® (n=149) Monovisc® (n=150) or saline (n=69). These 368 patients comprised the Safety Population and the ITT population. The Per-Protocol Population (PP) included all subjects who completed the 12 Week Visit and who had no major protocol deviations (n=335). Table 1 summarizes the baseline and patient demographic characteristics for the ITT population.

Table 1. Cingal 13-01 Demographic and Baseline Variables (ITT)

Characteristic	Parameter	Cingal®	Monovisc®	Saline	Combined
Age (Years)	n	149	150	69	368
	Mean	57.52	59.19	58.03	58.30
	Std. Dev.	8.39	8.62	9.02	8.62
	Median	57.00	59.00	58.00	58.00
	Minimum	40.0	40.0	40.0	40.0
	Maximum	72.0	74.0	75.0	75.0
	p-value	0.2337			
Gender n (%)	Male	52 (34.90)	51 (34.00)	18 (26.09)	121 (32.88)
	Female	97 (65.10)	99 (66.00)	51 (73.91)	247 (67.12)
	p-value	0.4122			

Table 1. Cingal 13-01 Demographic and Baseline Variables (ITT)

Characteristic	Parameter	Cingal®	Monovisc®	Saline	Combined
Race n (%)	Caucasian	149 (100.0)	149 (99.33)	69 (100.0)	367 (99.73)
	Other	0 (0.0)	1 (0.67)	0 (0.0)	1 (0.27)
	p-value	1.0000			
BMI (kg/m^2)	Mean	28.9	28.4	29.1	28.7
	Std. Dev.	4.7	4.5	4.5	4.6
	Median	28.4	27.9	28.8	28.4
	Minimum	19.3	19.1	21.5	19.1
	Maximum	39.4	39.9	39.2	39.9
	p-value	0.5047			
K-L Grade Index Knee n (%)	Grade I	36 (24.2%)	24 (16.0%)	17 (24.6%)	77 (20.9%)
	Grade II	84 (56.4%)	98 (65.3%)	38 (55.1%)	220 (59.8%)
	Grade III	29 (19.4%)	27 (18.0%)	14 (20.3%)	70 (19.0%)
	Grade IV	0 (0.0%)	1 (0.7%)	0 (0.0%)	1 (0.3%)
Baseline WOMAC Pain Score in Index Knee (mm)	Mean	58.9	61.0	58.8	59.7
	Std. Dev.	12.3	11.7	10.6	11.8
	Median	59.8	59.9	61.0	60.1
	Minimum	13.6	37.2	37.6	13.6
	Maximum	94.2	90.8	78.0	94.2
	p-value	0.2252			
Baseline WOMAC Pain in Contralateral Knee (mm)	Mean	11.5	11.9	10.3	11.4
	Std. Dev.	11.5	12.7	8.3	11.5
	Median	8.6	7.8	9.4	8.6
	Minimum	0.0	0.0	0.0	0.0
	Maximum	79.4	73.2	34.0	79.4
	p-value	0.6365			

Treatment and Evaluation Schedule:

Patients were followed for 26 weeks. Study visits were scheduled for screening, baseline, and weeks 1, 3, 6, 12, 18, and 26. Injections were performed aseptically at the baseline visit. Patients were required to discontinue all analgesics, including NSAIDs, for 7 days prior to the baseline visit and to accept "rescue" acetaminophen (up to a maximum of 4 grams per day) as the only medication for treatment of joint pain during the study. Rescue medication was not permitted within 48 hours of any study visit.

Safety Results:

Safety analyses were performed on the Safety Population, which was defined as all subjects who received treatment. A total of 217 Adverse Events (AEs) were recorded in the study, regardless of relatedness to Clinical Trial Material (CTM). There were 85 AEs in the Cingal® arm, 76 AEs in the Monovisc® arm, and 56 AEs in the saline arm. The Cingal® arm had 39.2% of the total AEs recorded, Monovisc® 35.0%, and saline 25.8%. These percentages are proportional with the study randomization (40% Cingal®; 40% Monovisc®; 20% saline).

The most common AEs regardless of relatedness to CTM (>5% of total AEs) were headache (15.7%), arthralgia (12.9%), spinal pain (8.3%), back pain (6.0%), and nasopharyngitis, or common cold (5.1%). Most (>99%) of the Adverse Events were rated as 'mild' or 'moderate' in severity. There were no significant differences among the study arms in the frequency and/or type of observed adverse events.

There were five Serious Adverse Events in four subjects (2 saline subjects and 2 Cingal® subjects); none of which were considered related to the CTM, and all of which resolved without sequelae.

There were a total of six Adverse Events considered related to the CTM (Table 2). The six related AEs (arthralgia, rash, and peripheral edema) were split between the Monovisc® and Cingal® arms and are common and transitory side effects seen with viscosupplements.

Table 2. Adverse Events related to Clinical Trial Material

Preferred Term	Cingal® (n=149) n	Monovisc® (n=150) n	Saline (n=69) n	Total (n=368) n
Arthralgia	2	2	0	4
Peripheral edema	1	0	0	1
Rash	0	1	0	1

Effectiveness Results:

Cingal 13-01 Study Measurements

Study measurements supporting the effectiveness endpoints were made at baseline and all subsequent study visits. The primary effectiveness endpoint was based on the change in WOMAC Pain Score from baseline. Table 3 summarizes the differences in WOMAC Pain from baseline by study visit for each treatment arm (ITT population).

Although the saline control arm demonstrates strong performance, Cingal® was statistically superior to saline at Follow-up Visits at Week 1, Week 3, Week 12, Week 18, and Week 26 in both ITT and PP populations. Cingal® achieved 72% improvement in WOMAC Pain Score at 26 weeks in the ITT population vs. 56% for saline and 65% for Monovisc®.

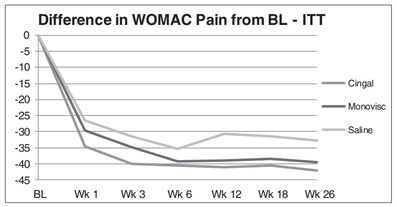
The data demonstrates that Cingal® is superior to Monovisc® at Week 1 and Week 3; supporting the usefulness of the corticosteroid in providing early pain relief. Both Cingal® and Monovisc® provide strong pain relief in Weeks 6 – 26, with no statistically significant differences between them in either the ITT or PP population. This data supports the long-term benefit provided by the HA viscosupplement.

Table 3. Change in WOMAC Pain Score from Baseline by Study Visit (ITT)

WOMAC Pain Score (ITT)	Baseline mean ± std. dev. (mm)	Difference from Baseline					
		Week 1 mean ± std. dev. (mm)	Week 3 mean ± std. dev. (mm)	Week 6 mean ± std. dev. (mm)	Week 12 mean ± std. dev. (mm)	Week 18 mean ± std. dev. (mm)	Week 26 mean ± std. dev. (mm)
Cingal®	**59.0** ±12.3	**-34.6** ±20.8	**-40.1** ±20.1	**-40.5** ±20.7	**-41.1** ±20.5	**-40.5** ±20.4	**-42.4** ±18.7
Monovisc®	**61.0** ±11.7	**-29.6** ±21.4	**-34.9** ±21.7	**-39.2** ±20.1	**-39.0** ±21.9	**-38.5** ±23.8	**-39.5** ±22.8
Saline	**58.8** ±10.6	**-26.6** ±18.2	**-31.4** ±18.8	**-35.5** ±20.2	**-30.8** ±23.7	**-31.4** ±24.2	**-32.9** ±23.6
P value Cingal® vs. Saline	-	**P=0.0080**	**P=0.0039**	P=0.0908	**P=0.0013**	**P=0.0059**	**P=0.0027**
P Value Cingal® vs. Monovisc®	-	**P=0.0367**	**P=0.0289**	P=0.5572	P=0.4103	P=0.4452	P=0.2525

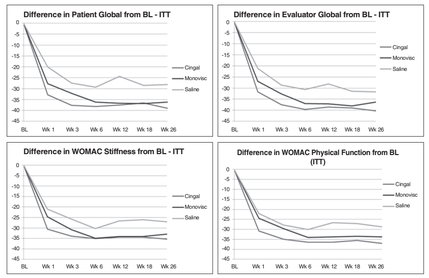
The data for the Change in WOMAC Pain Score from Baseline is portrayed graphically in Figure 2, below.

Figure 2. Change in WOMAC Pain Score from Baseline by Study Visit (ITT)



Results are graphed in Figures 3-6 below for the Changes from Baseline in Patient Global Assessment, Evaluator Global Assessment, WOMAC Stiffness Score, and WOMAC Physical Function Score. The results across all the measurements, whether patient-assessed or evaluator-assessed, are consistent.

Figures 3-6 Differences from Baseline for Additional Study Measurements



Cingal® is statistically superior to saline at almost every timepoint for measurements including pain, stiffness, physical function, and global assessment. Cingal® provides early pain and symptom relief compared to Monovisc® at Weeks 1 and 3. After Week 3 both Cingal® and Monovisc® provide similar, and strong, long-term pain relief and improvements in stiffness and physical function through 26 Weeks.

Cingal 13-01 Effectiveness Endpoint Results

- Cingal® met the primary endpoint and demonstrated superiority over saline for the change from baseline in WOMAC Pain Score through 12 weeks post treatment in both the ITT population (-40.2 mm vs. -31.0 mm, p=0.0099) and the PP population (-40.3 mm vs. -32.2 mm; p=0.0029).
- Cingal® met all secondary endpoints and the majority of exploratory endpoints relative to saline, demonstrating statistical superiority over saline for the following measures:
  - WOMAC Pain Score through 12 Weeks (ITT p< 0.01; PP p< 0.01)
  - WOMAC Pain Score through 26 Weeks (ITT p< 0.01; PP p< 0.01)
  - Patient Global Assessment through 12 Weeks (ITT p< 0.01; PP p< 0.01)
  - Patient Global Assessment through 26 Weeks (ITT p< 0.01; PP p< 0.01)
  - Evaluator Global Assessment through12 Weeks (ITT p< 0.01; PP p< 0.01)
  - Evaluator Global Assessment through 26 Weeks (ITT p< 0.01; PP p< 0.01)
  - OMERACT- OARSI Responders through 12 Weeks (ITT p=0.01; PP p=0.02)
  - OMERACT- OARSI Responders through 26 Weeks (ITT p=0.01; PP p=0.02)
  - WOMAC Stiffness Score through 26 Weeks (ITT p=0.01; PP p=0.01)
  - WOMAC Physical Function Score through 26 Weeks (ITT p=0.02; PP p< 0.01)
  - Total WOMAC Score through 26 Weeks (ITT p< 0.01; PP p< 0.01)
  - EuroQol VAS Health Scale through 26 Weeks (ITT p=0.04)
- Cingal® demonstrated superiority over Monovisc® at Week One and Week Three, confirming the early pain and symptom relief due to the corticosteroid, for the following secondary endpoints:
  - WOMAC Pain Score at One Week (ITT p=0.04; PP p< 0.01)
  - WOMAC Pain Score at Three Weeks (ITT p=0.03; PP p=0.02)
  - Patient Global Assessment at One Week (PP p=0.02)
  - Patient Global Assessment at Three Weeks (ITT p=0.03; PP p=0.01)
  - Evaluator Global Assessment at One Week (ITT p=0.04; PP p< 0.01)
  - Evaluator Global Assessment at Three Weeks (PP p= 0.01)

DETAILED DEVICE DESCRIPTION

Cingal® is a modification to the Health Canada-approved Monovisc® device (License number 80474), which consists of cross-linked hyaluronic acid (HA). The modification consists of inclusion of a steroid, triamcinolone hexacetonide (TH), approved by Health Canada as the active pharmaceutical ingredient (API) in Aristospan®. The HA viscosupplement provides the long term treatment of pain and symptoms through 26 weeks for patients with knee OA. The TH corticosteroid provides rapid relief of pain and symptoms over the first three weeks after the injection.

Cingal® is a biocompatible, non-pyrogenic, off-white, opaque, sterile suspension of the insoluble triamcinolone hexacetonide in the cross-linked hyaluronic acid gel from Monovisc®. Testing confirmed no physical or chemical changes to either the HA or TH upon formulation or after sterilization.

The device nominally contains 22.0 mg/mL high molecular weight cross-linked hyaluronic acid produced from bacterial fermentation, 4.5 mg/mL triamcinolone hexacetonide, excipients (sorbitol and polysorbate 80), buffers (sodium phosphate dibasic and sodium phosphate monobasic), and USP water for injection up to 100% volume. The cross-linked HA is identical to the material used in the Monovisc® formulation, and the TH and excipients are identical to the materials used in the Aristospan® formulation.

Each pre-filled syringe with 4 mL of Cingal® nominally contains:

Sodium Hyaluronate	88.0 mg
Triamcinolone Hexacetonide	18.0 mg
Sorbitol	200.0 mg
Polysorbate 80	8.0 mg
Sodium Phosphate, Dibasic	6.0 mg
Sodium Phosphate, Monobasic	1.2 mg
USP water for injection	q.s. to 4.0 mL

HOW SUPPLIED

Cingal® is supplied in a single-use 5 mL syringe containing a 4 mL dose of treatment. The contents of the syringe are sterile and non-pyrogenic. The syringe components do not contain latex.

DIRECTIONS FOR USE

Cingal® is injected into the knee joint and is administered as a single intra-articular injection. Standard intra-articular injection site preparation and precautions should be used. Strict aseptic administration technique must be followed.

1. Using an 18 – 20 gauge needle, remove synovial fluid or effusion before injecting Cingal® Do not use the same syringe for removing synovial fluid and for injecting Cingal® however, the same 18 – 20 gauge needle should be used.
2. Remove the protective rubber cap on the tip of the syringe and securely attach a small gauge needle (18 - 20 gauge) to the tip. Twist the tip cap before pulling it off, as this will minimize product leakage.
3. To ensure a tight seal and prevent leakage during administration, secure the needle tightly while firmly holding the luer hub. Do not over tighten or apply excessive leverage when attaching the needle or removing the needle guard, 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.

MANUFACTURED BY:

Anika Therapeutics, Inc.
32 Wiggins Avenue
Bedford, MA 01730
U.S.A.

Patient Information

Cingal®

What is Cingal®?

Cingal® is a viscous (thick) sterile mixture of hyaluronan with a steroid. The hyaluronan is highly purified and made from bacterial fermentation. Hyaluronan is a natural chemical found in the body. High amounts of hyaluronan are found in the joint tissues and in the fluid that fills the joints. The body's own hyaluronan acts like a lubricant and a shock absorber in the joint. It is needed for the joint to work properly. When you have osteoarthritis, there may not be enough natural hyaluronan in the joint, and the quality of that hyaluronan may be poorer than normal. Cingal® is used to supplement (add) hyaluronan to the knee joint. Cingal® also contains a steroid, triamcinolone hexacetonide, which provides short-term pain relief by reducing inflammation. Cingal® is given in a shot (injection) directly into the knee joint.

What is Cingal® used for?

Cingal® is used to relieve knee pain due to osteoarthritis. It is used for patients who do not get adequate pain relief from simple pain relievers like acetaminophen or from exercise and physical therapy.

What are the benefits of Cingal®?

Data from a clinical trial showed that Cingal® provides pain relief to patients who have not been able to find pain relief with simple pain medication or exercise.

What other treatments are available for osteoarthritis?

If you have pain due to osteoarthritis of the knee, there are things you can do that do not involve Cingal® injections.

These include:

Non-drug treatments:

- Avoiding activities that cause pain in your knee
- Exercise
- Physical therapy
- Removal of excess fluid from the knee

Medical Product therapy:

- Pain medication such as acetaminophen and narcotics
- Drugs that reduce inflammation, such as aspirin and other "nonsteroidal anti-inflammatory" agents (NSAIDs) (such as ibuprofen and naproxen)
- Corticosteroids that are injected directly into the knee joint
- Hyaluronic acid viscosupplements that are injected into the knee joint

Are there any reasons why you should not receive Cingal®?

- You should not take this product if you are allergic to hyaluronan products or to preparations containing triamcinolone hexacetonide.
- If you have any known allergies, you should consult with your healthcare professional to determine if you are able to have a Cingal® injection.
- You should not have an injection into the knee if you have infections or skin diseases around the injection site.

Things you should know about Cingal®

- Cingal® should be injected by a qualified physician or properly licensed practitioner.
- Tell your healthcare professional if you have any known allergies before Cingal® is administered.
- For 48 hours after you receive the injection, you should avoid activities such as jogging, tennis, heavy lifting or standing on your feet for a long time (more than one hour).
- The safety and effectiveness of Cingal® in joints other than the knee has not been demonstrated in U.S. studies.
- The safety and effectiveness of Cingal® has not been shown in pregnant or nursing women. You should tell your healthcare professional if you are pregnant or nursing.
- The safety and effectiveness of Cingal® has not been shown in children.
- The effectiveness of Cingal® has not been established for more than one course of treatment.

Possible complications

- Side effects are sometimes seen when Cingal® is injected into the knee joint. These can include: pain, swelling, heat, rash, itching, bruising and/or redness. You may also feel achy. The skin at the injection site may become thinner or change in color. You may experience facial flushing. These reactions are generally mild and do not last long.
- If any of these symptoms or signs appear after you are given Cingal® or if you have any other problems, you should call your healthcare professional.

How is Cingal® given?

Your healthcare professional will give a single injection of Cingal® (4 mL) into your knee.

Cingal® Manufacturer

Cingal® is manufactured by Anika Therapeutics, Inc., 32 Wiggins Avenue, Bedford, MA 01730.

AML 500-305 REV B

AML 500-305/B 12/2015

Cingal® Hyaluronic Acid plus Triamcinolone Hexacetonide, Intra-articular

AML 500-305/B 12/2015

AML 500-305/B