



Cingal

Fast Acting + Long Lasting

*A novel treatment for the pain
of knee osteoarthritis*



Anika. *Restore Active Living.*[™]

The first & only combination HA + steroid: powerful symptom relief in Week 1¹

Cingal[®] is the first and only approved combination viscosupplement formulated to provide the benefits of a cross-linked hyaluronic acid (HA) with a fast-acting steroid.

The formulation of Cingal allows for powerful long-term relief of the symptoms of osteoarthritis (OA) through 6 months¹. The cross-linked HA contributes to the viscoelastic properties of synovial fluid within the knee, reducing pain and improving function by means of lubrication and mechanical support.²

This is enhanced by the rapid anti-inflammatory action of micronized particles of Triamcinolone Hexacetonide (TH)², suspended in the viscoelastic HA, and residing within Cingal as a separate solid phase. The HA and TH do not physically or chemically interact⁴, ensuring maximum stability and efficacy of each compound and allowing Cingal to provide effective pain relief within the first few days of the injection being administered.¹

An independent study examined the effect on viscosity of mixing some corticosteroids or local anesthetics to HA. The addition of TH seemed to have no major deleterious effect on the viscosity level of cross-linked HA but the same could not be said of all corticosteroids or anesthetic agents when mixed with HA.⁵

Randomised double blind multi centre placebo controlled Phase 3 study¹

361 patients

Control 1 - Monovisc
150 patients

Control 2 - saline
69 patients

Cingal
149 patients

Results

- 59% improvement in WOMAC pain at Week 1 relative to baseline ($p = 0.008$)¹
- 72% improvement in WOMAC pain at Week 26 relative to baseline ($p = 0.0072$)¹
- 89% responder rate in the OMERACT-OARSI Responder Index at 1 Week ($p = 0.0161$)¹
- 92% responder rate in the OMERACT-OARSI Responder Index through 26 Weeks ($p = 0.0100$)¹

Conclusion

Cingal provided statistically significant faster pain relief compared to our market leading Monovisc HA in weeks one and three.¹ Cingal[®] demonstrated an excellent safety profile in the study. There were no Serious Adverse Events related to Clinical Trial Material (CTM), and only six adverse events considered related to CTM.

Potent anti-inflammatory effect of TH sustained for up to 21 days³

Rapid & sustained pain relief¹

Maximum chemical stability of HA and TH components to ensure efficacy^{4,6}

Strong safety profile in both initial and repeat injections^{1,7}

Improve outcomes in OA of the knee: delay reconstructive surgery by 3 years⁸

Cingal is designed for active people who need fast pain relief and prefer a single visit treatment. If your patients demand quick results to return their activities, want to remain active, or are looking to delay reconstructive surgery, Cingal may be an optimal treatment.



A retrospective database evaluation
of 182,022 TKR patients.⁸

27.7% were classified as HA Users, receiving minimum 1
course of HA prior to TKR

72.3% were HA Non-users prior to TKR

50% of HA Non-users had a TKR by **114 days** post-
diagnosis of knee OA, a mean time-to-TKR of 0.7 years

50% of HA Users had a TKR by **484 days** post-diagnosis

One course of HA - mean time to TKR was **1.4 years**

Five courses delayed TKR by **3.6 years**

**HA injections are therefore associated
with delay of TKR.**

The combination of rapid pain relief provided by TH and a delay to TKR thanks to a proven HA, makes Cingal a powerful choice for patients suffering from the chronic pain associated with OA of the knee.

Why is Cingal the right choice for your patient?

“ CINGAL combines two proven, approved therapies for pain and inflammation into a single injection treatment that has been shown to provide immediate pain relief that lasts for 6 months, reduce stiffness, and improve function. For knee pain sufferers, the availability of CINGAL not only translates to postponing an invasive and costly knee replacement surgery, but also to enabling these individuals to resume their normal lifestyle prior to the onset of chronic pain.”

Prof. Laszlo Hangody

Clinical Professor at the Semmelweis Medical School Budapest, former President of the Hungarian Orthopedic Society, and global principal investigator for the CINGAL Phase III program

How does Cingal work?

FAST ACTING CORTICOSTEROID TRIAMCINALONE HEXACETONIDE (4.5 mg/mL)²

Well established FDA approved steroid with potent anti-inflammatory effect to reduce pain quickly

HIGH CONCENTRATION & HIGH DOSE OF HA²

(22 mg/mL, 88mg total dose) creates a high viscosity environment to replicate healthy joint function, lubricating cartilage surfaces, allowing bones to glide smoothly and alleviating the symptoms of OA

OPTIMAL HIGH MOLECULAR WEIGHT HA

Results in greater pain reduction and longer duration of effect than low molecular weight or excessively high molecular weight HA³

LIGHTLY CROSS-LINKED HA

Leads to a more durable material that remains in the body for a longer period and has enhanced mechanical properties to absorb the shock of normal activities like walking and running.⁶

ULTRA PURE NON-AVIAN HMW HA

Produced via bacterial fermentation², no risk of developing allergic reactions to animal proteins-total of 6 Adverse Events related to CTM, 3 affecting Cingal patients, all resolved without sequelae¹

Indications

Cingal is indicated as a viscoelastic supplement or a replacement for synovial fluid in human knee joints. Cingal is well suited for rapid and long term relief of the symptoms of human knee joint dysfunctions such as osteoarthritis. The actions of Cingal are long term relief of symptoms by lubrication and mechanical support supplemented by short-term pain relief provided by triamcinolone hexacetonide.

Directions For Use

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. Store at 2 to 25°C. Protect from freezing. Refrigerated Cingal should be allowed to reach room temperature (approx. 20-45 min.) prior to use. Only medical professionals trained in accepted injection techniques for delivering agents into the knee joint should inject Cingal for the indicated use. For complete product information, including indications, contraindications, warnings, precautions, possible complications, and product storage, refer to product IFU.

Contents

The product contains 22 mg/mL high molecular weight cross-linked hyaluronic acid produced from bacterial fermentation, 4.5 mg/mL triamcinolone hexacetonide.

How Supplied

Cingal is supplied as a 4 mL unit dose in a terminally-sterilized 5 mL glass syringe.

The information contained in this document applies exclusively to territories outside of U.S.A.

References

1. CINGAL 13-01, a randomized, double-blind, placebo-controlled, active comparator Phase III study. Anika Therapeutics, Inc.: study sponsor, Dr. Laszlo Hangody: global principal investigator, Synteract HCR: CRO. 2. Cingal Instructions for use 3. Stephens M., et al. Musculoskeletal Injections: A Review of the Evidence. Am Fam Physician. 2008 Oct 15;78(8):971-976. Web: <http://www.aafp.org/afp/2008/1015/p971.html> 4. R009-041, Technical Report, "Chemical Stability Evaluation of Cross-Linked Hyaluronic Acid and Triamcinolone Hexacetonide in Cingal Product", December 2009. Appendix II of the device dossier. 5. Conrozier et al. Steroids, lidocaine and ioxaglic acid modify the viscosity of hyaluronic acid: in vitro study and clinical implications Springer Plus (2016) 5:170 DOI 10.1186/s40064-016-1762-z 6. Anika Proprietary data on file 7. CINGAL 13-02, an open-label, follow-on study to Cingal 13-01. Anika Therapeutics, Inc.: study sponsor, Dr. Laszlo Hangody: global principal investigator, Synteract HCR: CRO. 8. Altman R., Lim S., Steen R., Dasa V. Hyaluronic Acid Injections Are Associated with Delay of Total Knee Replacement Surgery in Patients with Knee Osteoarthritis: Evidence from a Large U.S. Health Claims Database. Osteoarthritis and Cartilage, Volume 23, A403 – A404; 2015 Dec. 9. Balazs, E.A. (1974). The physical properties of synovial fluid and the special role of hyaluronic acid. In Disorders of the Knee. (Ed. Helfet, A.) T.B. Lippincott

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