DUROLANE®
hyaluronic acid, stabilized single injection

bioventus®

# The original single injection for osteoarthritis pain relief

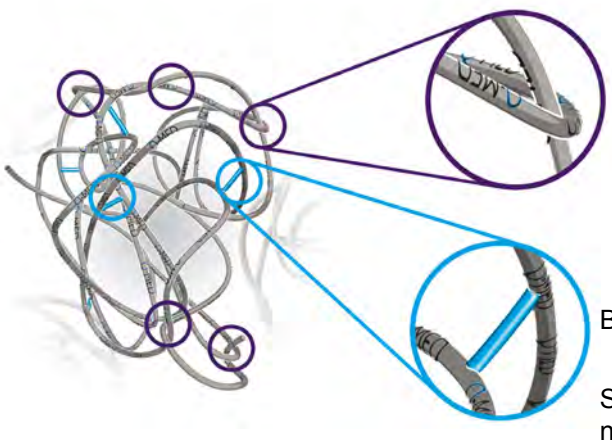
Since 2001*

*First introduced in the European Union in 2001

# DUROLANE® advanced and unique NASHA® technology[1]

## DUROLANE is a stabilised hyaluronic acid (HA), from a non-animal source, therapy for the intra-articular treatment of mild to moderate osteoarthritis in joints of all sizes.[2]

DUROLANE uses advanced and unique NASHA technology which gives it a unique gel bead structure. The patented* stabilisation technique ensures that the naturally cross-linked and entangled HA network is kept in place by introducing a very limited number of synthetic cross-links, resulting in minimal modification.



### NASHA structure

Entanglement of HA chains (natural cross-links)

BDDE (1, 4 butanediol diglycidyl ether) Linker

Stabilised HA: 1% stabilisation forms a flexible molecular network which resists physiological catabolism.[3]

*Patent available in certain countries

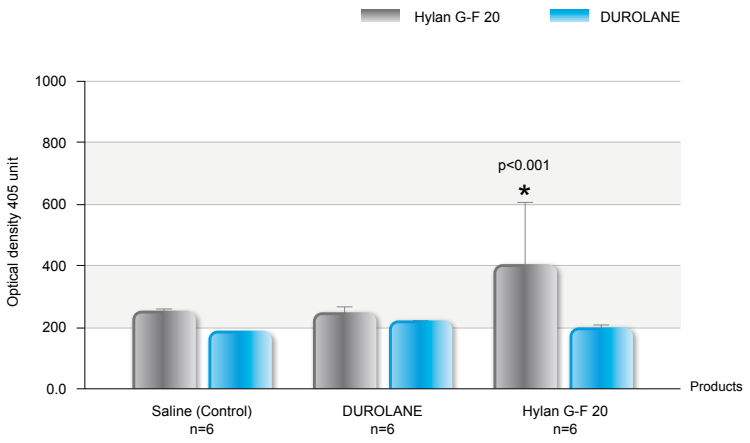
For intra-articular needle placement in knees with no effusion, an accuracy rate of 93% has been reported using a lateral midpatellar extended-leg injection approach.[17]

# A history of safe use[5]

## DUROLANE does not generate product specific antibodies[6]

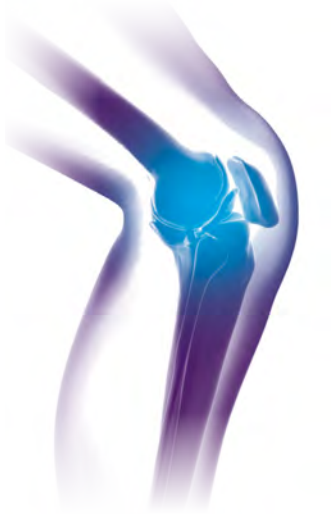
Mice were injected with different HA products under the skin in an air pouch. Then blood samples were obtained to test for antibody production.

- Antibody levels in DUROLANE treated animal blood were no different to controls
- DUROLANE did not cause a systemic immune response
- Antibody levels in Hylan G-F 20 treated animal's blood were significantly greater (p< 0.001) than saline or DUROLANE
- Hylan G-F 20 stimulated a systemic immune response




Antibody Binding to Viscosuplements,as seen with increased optical density. Mean ± SEM (Standard Error of the Mean)

# Significant and sustained benefits for hip[4,7] and knee OA patients[5]



## Effectiveness in comparison to corticosteroid[16]

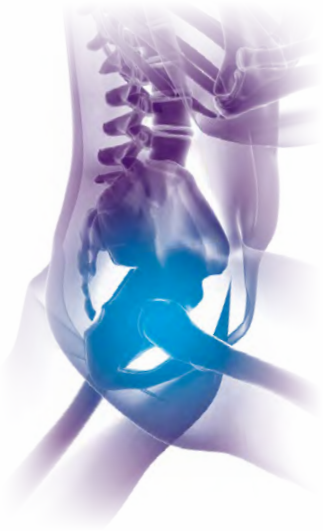
A randomised, blinded trial comparing one HA injection to corticosteroid for knee osteoarthritis pain;

- The pain relief effect measures in WOMAC pain responder rate (patients, %) of DUROLANE was shown to be non-inferior to methylprednisolone over 12 weeks.
- Based on the improvement from baseline, DUROLANE has shown to be longer lasting than methylprednisolone steroid at 26 weeks post-single injection treatment (p=0.034).

## Effectiveness in hips

Significant ($p<0.05$) improvements at six months following injection under fluoroscopic control:[7]

- Forty patients with hip OA were treated with a single intra articular injection of DUROLANE.
- Walking Pain, Patient Global Assessment, WOMAC A & B decreased significantly between baseline and six months.
- 71% were classified OMERACT-OARSI responders.

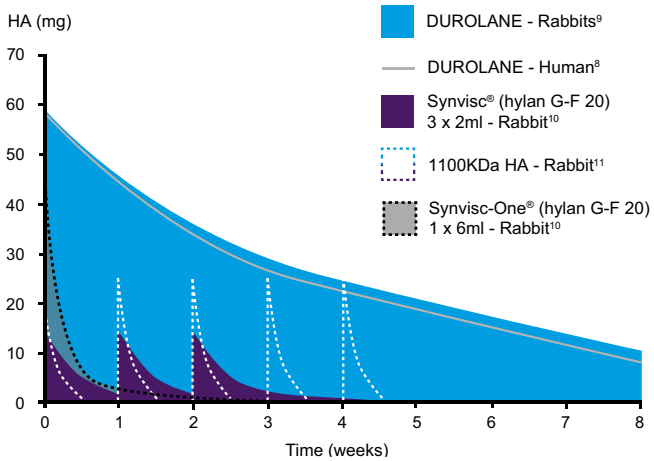


# Long lasting by design[1]

## DUROLANE uses unique and advanced NASHA technology to increase residence time in the joint[8,9]

Data from human and animal studies have shown that:

- DUROLANE has a half-life of 4 weeks or 32 days in the joint in a single injection treatment regime[8,9]
- DUROLANE has a longer half-life than unstabilized hyaluronic acid (HA) and cross-linked Synvisc® (hylan G-F 20)[10,11]

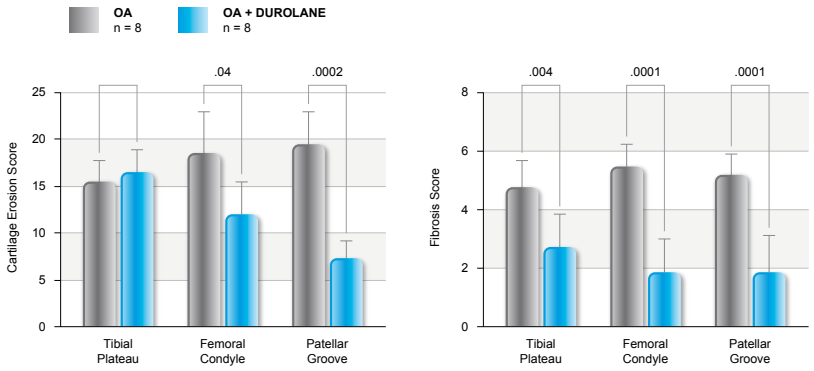



Graphs based on elimination of hyaluronic acid (HA) from the joint space of rabbits as a function of time for DUROLANE[9] as compared against extrapolated data for the residence time of hylan G-F 20[10] and low molecular weight HA[11] in a similar rabbit model. DUROLANE values calculated based on projected clearance of one-3ml injection (20mg/ml). Hylan G-F 20 values calculated based on projected clearance of one-6ml injection (representing Synvisc-One®) or three-2.0ml injections (representing Synvisc®-3 injection regimen) of HA at 16 mg/ml in a rabbit model.[10] As shown in the graph, DUROLANE human data correlates well with the rabbit model.[8]

* At this time there is no known evidence to indicate whether there is any correlation between the residency period of HA in a joint and the safety or efficacy of HA to treat a joint.

# Pre-clinical evidence for the efficacy of DUROLANE

## DUROLANE prevented knee osteoarthritis progression in an animal model[12]

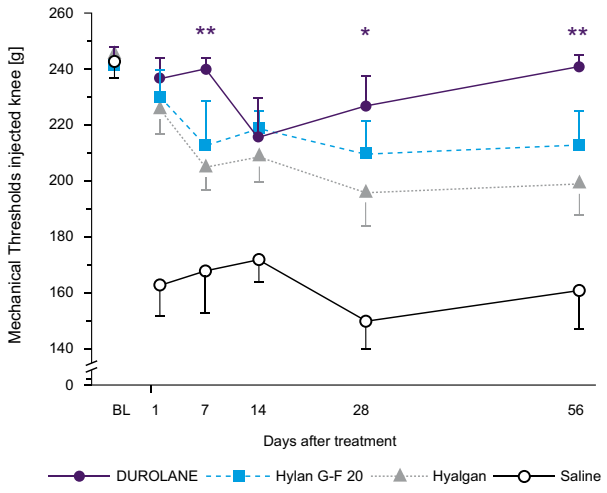



In an OA model:

- DUROLANE injection protected joints from femoral cartilage erosion as well as tibial and femoral tissue fibrosis (see graph).
- DUROLANE maintained the gait pattern (Stance time) to that observed prior to the experiment, whereas animals treated with saline had worsening gait pattern, as observed by increasing stance time.
- Both DUROLANE injection and saline injection reduced pain in allodynia score, but the DUROLANE effect was more pronounced and prolonged than the saline injection.

Joint Tissue Pathology Scores showing the protective effects of prophylactic hyaluronan (HA) on murine joint osteoarthritis (OA). (a) Cartilage erosion scores and (b) fibrosis scores for the OA (n=8 ± standard deviation) and OA + DUROLANE (n=8 ± standard deviation) groups illustrates the statistically significant and area-specific effects of DUROLANE on murine OA pathology.

## DUROLANE provided superior pain relief, compared to Synvisc®, in an animal knee joint pain model[13]




Mechanical threshold data (means ± SEM) for the affected limb. The mean force required to cause withdrawal for the morphine group was 246.3g. Base = Baseline testing.

DUROLANE was compared to other HA preparations* and a saline control:

- The saline control was least effective at pain relief shown by the least amount of pressure applied to the knee joint after injection to induce a response.
- The pain relief DUROLANE provided was significantly better than unmodified sodium hyaluronate and Hylan G-F 20 at multiple time points (* $p<0.05$: ** $p<0.01$)
- A single injection of DUROLANE provided pain relief out to 56 days in this animal knee pain model

Primary mechanical pain threshold was assessed following an injection of pain inducing agents by ascending pressure applied to the animal knee joint, after a single injection of NASHA (50 µl, n = 11), Hylan G-F 20 (100 µl, n = 9), and sodium hyaluronate (33 µl, n = 11). Although saline-treated animals showed a dramatic drop in mechanical thresholds from day 1, all hyaluronic acid compounds showed antinociceptive properties. These were most pronounced for NASHA and hylan G-F 20, which were superior to unmodified sodium hyaluronate, particularly in the later stages.

* Preparations used included: NASHA (DUROLANE), Hylan G-F 20 (Synvisc®) and unmodified sodium hyaluronate (Hyalgan®).

**NOTE:** Clinical dosage of Hyalgan® is three or five injections. Model utilizes single injection.

# Effective relief from osteoarthritis pain with one safe treatment[14-16]

## DUROLANE is a single-injection treatment to relieve the pain of osteoarthritis in specific small and large joints.[2] It is based upon a safe and proven technology of stabilised hyaluronic acid, NASHA. Hyaluronic acid (HA) is a naturally occurring molecule that provides the lubrication and cushioning in a normal joint.

DUROLANE is a sterile, transparent viscoelastic gel supplied in either a 1ml or 3ml glass syringe with a luer-lok fitting, packed in a blister pack.

DUROLANE contains 20mg/ml of stabilised, non-animal hyaluronic acid (NASHA) in buffered physiological sodium chloride solution pH7.

DUROLANE is a single dose preparation and should only be injected once per treatment course.

DUROLANE is indicated* for the symptomatic treatment of mild to moderate osteoarthritis.

- Based on the improvement from baseline, DUROLANE has shown to be longer lasting than methylprednisolone steroid at 26 weeks post-single injection treatment (p=0.034).[16]
- Patients that received two DUROLANE injections had a 38% reduction from baseline in WOMAC pain score at 26 weeks, prior to the second injection and nearly 50% at 52 weeks.[16]
- After second injections of DUROLANE no allergic reactions have been observed.[16]

## Product Information

Productcode:

- DUROLANE (3ml) 1082010
- DUROLANE (1ml) 1082004

*** Summary of Indications for Use**

**DUROLANE (3ml):** Symptomatic treatment of mild to moderate knee or hip osteoarthritis. In addition, DUROLANE has been approved in the EU for the symptomatic treatment associated with mild to moderate osteoarthritis pain in the ankle, shoulder, elbow, wrist, fingers, and toes.

**DUROLANE SJ (1ml):** Symptomatic treatment associated with mild to moderate osteoarthritis pain in the ankle, elbow, wrist, fingers, and toes.

Both DUROLANE and DUROLANE SJ are also indicated for pain following joint arthroscopy in the presence of osteoarthritis within 3 months of the procedure.

There are no known contraindications.

You should not use DUROLANE if you have infections or skin disease at the injection site. DUROLANE has not been tested in pregnant or lactating women, or children. Risks can include transient pain, swelling and/or stiffness at the injection site.

Full prescribing information can be found in product labeling, or at www.durolane.com.

## References


**1.** Agerup B, Berg P, Åkermark C. Non-animal stabilized hyaluronic acid: a new formulation for the treatment of osteoarthritis. *BioDrugs.* 2005;19(1):23-30. **2.** DUROLANE Product Insert: 3ML (Dec. 2013) and SJ 1ML (Dec. 2013). **3.** Edsman K, Melin H, Näsström J. A study of the ability of Durolane to withstand degradation by free radicals while maintaining its viscoelastic properties. Poster presented at: 55th Annual Meeting of the Orthopaedic Research Society; February 2009; Las Vegas, NV. **4.** Berg P, Olsson U. Intra-articular injection of non-animal stabilised hyaluronic acid (NASHA) for osteoarthritis of the hip: a pilot study. *Clin Exp Rheumatol.* 2004;22(3):300-6. **5.** RPT-000374 Data on File MA 12414 – Report of Prior Clinical Investigations DUROLANE. **6.** Wooley P, Song Z, Harrison A. Evaluation of the Biocompatibility of Durolane using the Murine Air Pouch Model. Poster presented at: 55th Annual Meeting of the Orthopaedic Research Society; February 2009; Las Vegas, NV. **7.** Conrozier T, Couris CM, Mathieu P, et al. Safety, efficacy and predictive factors of efficacy of a single intraarticular injection of non-animal-stabilized-hyaluronic-acid in the hip joint: results of a standardized follow-up of patients treated for hip osteoarthritis in daily practice. *Arch Orthop Trauma Surg* (2009) 129:843–848. **8.** Lindqvist U, Tolmachev V, Kairemo K, et al. Elimination of stabilised hyaluronan from the knee joint in healthy men. *Clin Pharmacokinet.* 2002;41(8):603-613. **9.** Edsman K, Hjelm R, Lärkner H, et al. Intra-articular Duration of Durolane after Single Injection into the Rabbit Knee. *Cartilage.* 2011; 2(4) 384–388. **10.** Larsen NE, Dursema HD, Pollak CT, Skrabut EM. Clearance kinetics of a hylan-based viscosupplement after intra-articular and intravenous administration in animal models. J *Biomed Mater Res B Appl Biomater.* 2012; 100(2):457-466. **11.** Brown TJ, Laurent UB, Fraser JR. Turnover of hyaluronan in synovial joints: elimination of labelled hyaluronan from the knee joint of the rabbit. *Exp Physiol.* 1991; 76(1):125-134. **12.** Plaas A, Li J, Riesco J, Das R, Sandy JD, Harrison A. Intraarticular injection of hyaluronan prevents cartilage erosion, periarticular fibrosis and mechanical allodynia and normalizes stance time in murine knee osteoarthritis. *Arthritis Res Ther.* 2011;13(2):R46. **13.** Boettger MK, Kümmel D, Harrison A, Schaible HG. 'Evaluation Of Long-Term Antinociceptive Properties Of Stabilized Hyaluronic Acid Preparation (NASHA) In An Animal Model Of Repetitive Joint Pain'. Arthritis Research & Therapy 13.4 (2011): R110. **14.** Krocker D, Matziolis G, Tuischer J, et al. Reduction of arthrosis associated knee pain through a single intra-articular injection of synthetic hyaluronic acid. *Z Rheumatol.* 2006; 65(4):327-31. **15.** Åkermark C, Berg P, Björkman A, Malm P. Non-Animal Stabilised Hyaluronic Acid in the Treatment of Osteoarthritis of the Knee A Tolerability Study. *Clin Drug Invest* 2002; 22 (3): 157-166. **16.** Leighton R, Åkermark C, Therrien R, et. al. NASHA hyaluronic acid vs methylprednisolone for knee osteoarthritis: a prospective, multi-centre, randomized, non-inferiority trial. *Osteoarthritis & Cartilage.* 2014;22(1):17-25. **17**. Jackson D, Nicholas E, and Bradley T. 'Accuracy Of Needle Placement Into The Intra-Articular Space Of The Knee'. *The Journal of Bone & Joint Surgery* 84.9 (2002): 1522-1527.



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