DUROLANE® en
INSTRUCTIONS FOR USE

INFORMATION FOR PRESCRIBERS

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

DESCRIPTION
DUROLANE is a clear, transparent, viscous gel of highly purified, stabilized, non-animal-derived sodium hyaluronate that is biosynthesized using bacterial fermentation. NASHA® technology is used to stabilize naturally entangled hyaluronic acid (HA) chains to produce a gel. The gel is suspended in phosphate-buffered saline at a concentration of 20 mg/mL.

INDICATIONS
DUROLANE is indicated for the treatment of pain in osteoarthritis (OA) of the knee in patients who have failed to respond adequately to conservative non-pharmacological therapy or simple analgesics, e.g. acetaminophen.

CONTRAINDICATIONS
- Do not inject DUROLANE with knee joint infections, infections, or skin disease in the area of the injection site.
- Do not administer to patients with known hypersensitivity (allergy) to HA preparations.

WARNINGS
- Do not concomitantly use disinfectants containing quaternary ammonium salts for skin preparation because sodium hyaluronate can precipitate in their presence.
- Do not inject intra-vascularly, extra-articularly, or in the synovial tissues or capsule.

PRECAUTIONS
General

- The safety and effectiveness of DUROLANE in joints other than the knee have not been studied.
- The effectiveness of repeated injection cycles of DUROLANE has not been established.
- Remove any joint effusion before injecting DUROLANE.
- Transient pain or swelling of the injected joint may occur after intra-articular injection with DUROLANE.
- STERILE CONTENTS. EXTERIOR OF SYRINGE IS NOT STERILE. The contents of the syringe must be used immediately after its packaging is opened. Do not re-sterilize the product.
- Strict aseptic administration technique must be followed.
- Do not re-use. Dispose of the syringe and any unused DUROLANE after use.
- Do not use if the syringe blister package is opened or damaged.
- The route for intra-articular injection should be chosen so that damage to adjacent vital structures is avoided.
- An increase in injection pressure may indicate incorrect extra-articular placement of the needle or overfilling of the joint.
- Local anesthetics should not be used if the patient is known to be allergic or sensitive to local anesthetic.
- DUROLANE should be used with caution in patients with pre-existing chondrocalcinosis as injection may lead to an acute attack of the condition.
- As with any viscosupplementation treatment, the patient should avoid any strenuous activities or prolonged (i.e. more than an hour) weight bearing activities within 48 hours following intra-articular injection.

USE IN SPECIFIC POPULATIONS
- Pregnancy: The safety and effectiveness of the use of DUROLANE have not been established in pregnant women.
- Nursing mothers: The excretion of DUROLANE in human milk is not known. The safety and effectiveness of DUROLANE have not been established in lactating women.
- Pediatrics: The safety and effectiveness of DUROLANE have not been established in children (21 years of age or younger).

POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH
Potential adverse effects (e.g., complications) associated with the use of this device and, in general, associated with intra-articular injection devices for the treatment of pain in osteoarthritis of the knee, include:

- Aggravated osteoarthritis
- Arthralgia (knee pain)
- Arthropathy
- Arthrosis
- Baker's cyst
- Bursitis
- Immune response
- Infection
- Injection site erythema
- Injection site edema
- Injection site pain
- Injection site reaction
- Localized osteoarthritis
- Joint (knee) disorder
- Joint (knee) effusion
- Joint (knee) stiffness
- Joint (knee) swelling
- Pain in limb
- Paraesthesia
- Phlebitis
- Pruritus
- Tendonitis

Incidences of rash, headache, dizziness, chills, hives, nausea, muscle cramps, peripheral edema, and malaise have also been reported in association with intra-articular injections.

A summary of the frequency and rate of adverse events identified in the clinical studies associated with DUROLANE's clinical development is provided in the "Clinical Studies" section.

CLINICAL STUDIES
Original Clinical Development Studies

The original clinical development of DUROLANE was founded upon three randomized, controlled trials: 35GA0001, 35GA0301, and 35GA0608. The initial two trials were superiority studies versus saline; the third was a non-inferiority trial versus the commonly used corticosteroid, methylprednisolone acetate (MPA). All trials evaluated the outcome measure associated with a pain responder rate, defined as a minimum 40% reduction from baseline in Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain scores and an absolute reduction of at least 5 points in that score.

The saline controlled trials are summarized in **Table 1**.

Neither of these saline-controlled studies demonstrated superiority over saline. Confounding factors were identified following subgroup analyses after completion of each trial. Study 35GA001 included patients with polyarticular pain, making it difficult to discriminate if pain reported was from the signal knee joint versus other joints. Study 35GA0301 identified an additional confounding factor of joint effusion. The presence of effusion may signify the presence of an active inflammatory process which can lead to degradation of HA through proinflammatory cytokine activity.

These two studies informed the design of the third study, 35GA0608, outside of the United States, comparing DUROLANE versus MPA. Results from this study are summarized in **Table 2**.

Adverse events from these three trials are collectively presented in **Table 3**.

Repeated Injection Safety of DUROLANE

The safety of the repeated use of DUROLANE is supported by one open label study conducted at two centers in Sweden, 35GO9901E, and an extension phase to the non-inferiority trial versus MPA, 35GA0608. In 35GO9901E, patients were offered a second injection of DUROLANE 3 months following the initial injection and 26-weeks post-injection in 35GA0608. The adverse event rates of the three groups were comparable, and the adverse events (AEs) from these studies are summarized in **Table 4**.

Pivotal Clinical Dataset: Comparative Study of Safety and Efficacy of Two Hyaluronic Acids for the Treatment of Knee Osteoarthritis – TG1018DLN

Study Design

Study TG1018DLN was a prospective, randomized, controlled, multicenter clinical study intended to demonstrate that DUROLANE was non-inferior to a commercially-available, 5-injection regimen HA product in the treatment of pain associated with knee OA over 26 weeks. A total of 349 patients were evaluated at 7 centers in the People's Republic of China. The primary outcome measure was based on the WOMAC 20-point Likert-scale. The non-inferiority margin was established as 8% (i.e., +1.6 units of the Likert-scale). Other outcome measures collected included WOMAC subscale domains of stiffness and physical function, along with subject global assessment.

Study Population

Study patients had a documented diagnosis of mild to moderate OA of the knee per the American College of Rheumatology criteria, were 40 to 80 years old, and had either Grade II or Grade III OA of the knee according to the Kellgren-Lawrence (KL) radiographic scale. Patients with KL Grades 0, I or IV, poly-articular pain, or clinically palpable knee effusions were excluded. Patients were required to have a WOMAC score between 7 and 17 at the screening and baseline visits.

Patients were randomized in a 1:1 ratio to receive either a single injection of DUROLANE or a regimen of 5-injections of the commercially available HA over the course of 5 weeks.

Demographic and baseline characteristics were balanced between the two groups; see **Table 5**.

Study Treatment and Evaluation Schedule

Patients were followed for 26 weeks. Effectiveness was assessed at Weeks 6, 10, 14, 18, and 26. Safety was assessed at screening and at Weeks 0, 1, 2, 3, 4, 6, 10, 14, 18, and 26. To address patient blinding due to the different injection regimens for the products, the DUROLANE group was given 3 mL at Week 0 (baseline) and received subcutaneous skin punctures (i.e., the needle did not enter the joint space) with an empty syringe at Weeks 1, 2, 3, and 4. The 5-injection HA group was administered using 2.5 mL injections of product at the same five time points.

Before the baseline visit, the current use of analgesics was required to have elapsed by at least 5 half-lives; within 48 hours before each visit, patients were not allowed to take any acetaminophen (paracetamol) or any other analgesic. Acetaminophen was permitted as rescue analgesia during the course of the study.

Safety Results

The safety set was comprised of 175 DUROLANE and 174 5-injection HA subjects. Subjects with at least one treatment emergent AE were 47.4% and 42.5% in the DUROLANE and the 5-injection HA groups, respectively. The most common of these were musculoskeletal and connective tissue disorders in both groups (DUROLANE: 25.1%; 5-injection HA: 22.4%).

Subjects with device-related AEs were 13.1% and 9.8% in the DUROLANE and the 5-injection HA groups, respectively. The most common device-related AE was arthralgia for both groups (DUROLANE: 8.6%; 5-injection HA: 7.5%).

The severities of device-related AEs in both groups were mainly mild and moderate; only one case of injection site pain in the DUROLANE group and two cases of arthralgia and one case of joint swelling in the 5-injection HA group were classified as severe.

The percentage of subjects with Serious Adverse Events (SAEs) was 1.7% (3/175) and 3.4% (6/174) in the DUROLANE and the 5-injection HA groups, respectively. No SAEs were considered related to the investigational products.

No deaths occurred in this study.

A summary of AEs in the safety set is outlined in **Table 6**.

A summary of device-related AEs is outlined in **Table 7**.

Effectiveness Results

The results demonstrated that DUROLANE was non-inferior to the 5-injection HA. The Least Squares Mean (LSM) WOMAC pain subscale score Change from Baseline (CFB) over 18 weeks was -5.97 for DUROLANE and -5.87 for the 5-injection HA, with a difference (DUROLANE-5-injection HA) of -0.09 (95% CI: -0.58, 0.39). As the upper bound of the confidence interval did not exceed the pre-specified non-inferiority margin of +1.6, non-inferiority was established (**Figure 1**). See **Table 8** for a tabular summary of the results of the primary endpoint by visit.

The same 8% non-inferiority margin utilized for the primary effectiveness variable was used for all secondary variables. Results through 26 weeks for the WOMAC pain subscale score CFB are included in **Table 8**.

The remaining secondary variables were tested for non-inferiority in a stepwise order as outlined in **Table 9**. All secondary effectiveness outcomes met the 8% non-inferiority criteria over the course of the study.

BENEFIT-RISK ANALYSIS
A single injection of DUROLANE provides a benefit for pain reduction in patients with osteoarthritis in the knee for up to 26 weeks. An additional benefit of DUROLANE is the ability for patients to be treated with a single injection versus a series of injections required of other multi-injection HA formulations. The results of the pivotal clinical trial supported the conclusion that the benefits of DUROLANE in treating pain due to osteoarthritis of the knee outweigh the risks of transitory adverse events such as pain and swelling.

DETAILED DEVICE DESCRIPTION
DUROLANE is a high molecular weight, non-animal, stabilized gel manufactured using NASHA technology. The device is administered as a single injection.

Each 3 mL glass syringe of DUROLANE contains 20mg/mL of sodium hyaluronate, dissolved in phosphate buffered saline. The sodium hyaluronate is derived from bacterial fermentation (Streptococcus equi).

Each pre-filled syringe contains the following:

Component	Each mL contains
Stabilized Sodium Hyaluronate	20 mg
Sodium Chloride	9 mg
Potassium Dihydrogen Phosphate	0.03 mg
Disodium Hydrogen Phosphate Dihydrate	0.14 mg
Water for Injection	q.s. 1 mL

HOW SUPPLIED
DUROLANE is supplied in a 3 mL, single-use glass syringe with a Luer-lok fitting, packed in a blister pack. The gel contents of the syringe have been sterilized; the exterior surfaces of the syringes are non-sterile. A needle (18-22 G) with adequate length is to be used to inject the gel into the knee joint (intra-articular space). The needle is not provided in the product package.

SHELF LIFE
36 months. DUROLANE must be used prior to the expiry date printed on the package.

STORAGE INSTRUCTIONS
DUROLANE should be stored, in its original packaging, between 0-30ºC (32-86ºF). Transient spikes up to 40ºC (104ºF) are permitted as long as they do not exceed 24 hours. Protect from freezing. Refrigeration is not needed.

DIRECTIONS FOR USE
1. DUROLANE should only be injected into the diseased knee joint by an authorized physician or medical professional, familiar with intra-articular injection techniques, and in facilities well suited for intra-articular injections.
2. Prepare the injection site by swabbing the site with alcohol or another suitable antiseptic solution.
3. Use of topical or subcutaneous anesthetic may be recommended prior to injection.
4. Using an appropriate gauge needle, remove any joint effusion, if present. NOTE: If using the same needle for effusion removal and for injection of DUROLANE, the recommended needle size is 18 to 22G with adequate length. Use of smaller needles increases pressure required to deliver the product.
5. Following removal of any joint effusion, prepare product for injection; do not use if the blister package is opened or damaged.
6. To ensure a tight seal and prevent leakage during administration, secure the needle tightly while firmly holding the luer hub.
7. Inject the full contents of the syringe intra-articularly into the knee synovial capsule (i.e, 3 mL). If treatment is bilateral, use a separate syringe for each knee.
8. Discard any unused DUROLANE.
9. For single use only. Do not re-sterilize.

MANUFACTURER
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90-35807-01

DUROLANE® hyaluronic acid, stabilized single injection

bioventus®

Packaging Symbols

- Do not re-use
- Do not resterilize
- Temperature limit 0-30ºC (32-86°F)
- Do not use if package is damaged
- Caution
- Use-by date
- LOT Batch code
- Manufacturer
- Rx only CAUTION: U.S. Federal law restricts this device to sale by or on the order of a physician

90-35807-01

Table 1: Original Clinical Development Studies-DUROLANE vs. Saline

Clinical Study No.	n	# of Centers	Pain Responder Rate %			
			Visits	DUROLANE	SALINE	*p* value
35GA0001	DUROLANE: 172 Saline: 174	7 US 6 Canada 5 Sweden	2 weeks	29.1	36.2	0.16
			6 weeks	36.6	29.9	0.18
			3 months	32.0	35.1	0.54
			6 months	29.1	32.2	0.53
35GA0301	DUROLANE: 108 Saline: 110	6 Canada 4 United Kingdom 2 Germany	2 weeks	19.4	25.5	0.29
			4 weeks	26.9	26.4	0.94
			6 weeks	30.6	26.4	0.49

Table 2: Original Clinical Development Studies-DUROLANE vs. MPA

Clinical Study No.	# of Centers	Pain Responder Rate %			
		Visits	DUROLANE (n=221)	MPA (n=221)	Difference 95% Confidence Interval
35GA0608	15 Canada 5 Sweden 4 UK	6 weeks	47.7	50.2	(-11.9%; +6.9%)
		12 weeks	44.6	46.2	(-11.2%; +7.9%)
		18 weeks	43.0	45.2	(-11.9%; +7.4%)
		26 weeks	43.9	36.9	(-2.5%; +16.6%)

Table 3: Summary of Adverse Events Reported in Original Clinical Development Studies

Preferred Class*	DUROLANE All three studies (n=502)	MPA 35GA0608 (n=221)	Saline 35GA0001 & 35GA0301 (n=284)
	n (%)	n (%)	n (%)
Related to product or injection procedure or both			
Nausea	-	2 (0.9%)	-
Pyrexia	2 (0.4%)	-	-
Injection site haematoma	-	-	2 (0.7%)
Injection site haemorrhage	-	-	1 (0.4%)
Injection site pain	15 (3.0%)	1 (0.5%)	2 (0.7%)
Injection site swelling	2 (0.4%)	-	-
Blood glucose increased	1 (0.2%)	-	-
Arthralgia	54 (10.8%)	7 (3.2%)	8 (2.8%)
Arthropathy	9 (1.8%)	-	5 (1.8%)
Joint crepitation	1 (0.2%)	-	-
Joint effusion	1 (0.2%)	1 (0.5%)	-
Joint lock	1 (0.2%)	-	-
Joint stiffness	4 (0.8%)	-	-
Joint swelling	5 (1.0%)	1 (0.5%)	-
Joint warmth	1 (0.2%)	-	-
Muscle spasms	1 (0.2%)	-	-
Pain in extremity	1 (0.2%)	1 (0.5%)	-
Sensation of heaviness	-	1 (0.5%)	-
Synovitis	1 (0.2%)	-	1 (0.4%)
Anxiety	1 (0.2%)	-	-
Depression	1 (0.2%)	-	-
Dermatitis	-	-	1 (0.4%)
Headache	2 (0.4%)	-	-
Haemarthrosis	1 (0.2%)	-	-
Myalgia	1 (0.2%)	-	-
Oedema peripheral	-	-	1 (0.4%)
Osteoarthritis	2 (0.4%)	1 (0.5%)	-
Nervousness	1 (0.2%)	-	-

* AEs in the 35GA0001 and 35GA0301 studies were classified using World Health Organisation, Adverse Reaction Terminology (WHO ART). In 35GA0608, AEs were classified using Medical Dictionary for Regulatory Activities (MedDRA).

Table 4: Summary of Related Adverse Events Reported for Repeat Injections of DUROLANE

Preferred term*	35GA0608 1st injection: DUROLANE (n=163)	35GA0608 1st injection: MPA (n=179)	35GO9901E DUROLANE (n=53)
Related to product or injection procedure or both			
Arthralgia	30 (18.4%)	31 (17.3%)	9 (17.0%)
Arthropathy	-	-	2 (3.8%)
Joint dislocation	1 (0.6%)	-	-
Joint effusion	1 (0.6%)	-	-
Joint stiffness	1 (0.6%)	3 (1.7%)	-
Joint swelling	2 (1.2%)	1 (0.6%)	-
Joint warmth	-	1 (0.6%)	-
Musculoskeletal discomfort	3 (1.8%)	-	-
Urticaria	-	1 (0.6%)	-

* AEs in the 35GO9901E study were classified using World Health Organisation, Adverse Reaction Terminology (WHO ART) and Medical Dictionary for Regulatory Activities (MedDRA) for 35GA0608.

Table 5: Demographic data and baseline characteristics

		DUROLANE	5-injection HA	TOTAL
Variable		(n=161)	(n=158)	(n=319)
Age (years)	Mean (SD)	60.2 (8.1)	60.4 (7.8)	60.3 (7.9)
	Median	60	59	59
	Min; Max	40; 78	42; 78	40; 78
Sex [n (%)]	Female	119 (73.9)	127 (80.4)	246 (77.1)
	Male	42 (26.1)	31 (19.6)	73 (22.9)
	Total	161 (100.0)	158 (100.0)	319 (100.0)
Nationality [n (%)]	Han	155 (96.3)	157 (99.4)	312 (97.8)
	Other	6 (3.7)	1 (0.6)	7 (2.2)
	Total	161 (100.0)	158 (100.0)	319 (100.0)
Weight (kg)	n	161	158	319
	Mean (SD)	66.5 (10.2)	66.8 (10.8)	66.6 (10.5)
	Median	65.0	67.0	65.0
	Min; Max	44.0; 100.0	44.5; 106.0	44.0; 106.0
Height (cm)	n	161	158	319
	Mean (SD)	162.5 (6.7)	162.4 (7.7)	162.4 (7.2)
	Median	162	160	162.0
	Min; Max	147; 183	145; 190	145; 190
BMI (kg/m^2)	n	161	158	319
	Mean (SD)	25.1 (3.2)	25.3 (3.2)	25.2 (3.2)
	Median	24.8	25.1	25.0
	Min; Max	18.4; 33.9	19.0; 35.0	18.4; 35.0
BMI classification	Underweight	1 (0.6)	0 (0.0)	1 (0.3)
	Normal range	81 (50.3)	76 (48.1)	157 (49.2)
	Overweight	65 (40.4)	69 (43.7)	134 (42.0)
	Obese	14 (8.7)	13 (8.2)	27 (8.5)
	Total	161 (100.0)	158 (100.0)	319 (100.0)

Table 6: Summary of Adverse Events – Safety Set (SS)

	DUROLANE (n=175)	5-injection HA (n=174)
	n (%)	n (%)
Subjects with at least one treatment emergent AE	83 (47.4)	74 (42.5)
Subjects with device-related AEs	23 (13.1)	17 (9.8)
Subjects with a severe AE	6 (3.4)	8 (4.6)
Subjects with a SAE	3 (1.7)	6 (3.4)
Subjects with a device-related SAE	-	-
Death	-	-

Table 7: Device-Related Adverse Events

Primary System Organ Class (SOC) Preferred term	DUROLANE (n=175)	5-injection HA (n=174)
	n (%)	n (%)
General disorders and administration site conditions	4 (2.3)	2 (1.1)
Injection site pain	4 (2.3)	2 (1.1)
Musculoskeletal and connective tissue disorders	18 (10.3)	16 (9.2)
Arthralgia	15 (8.6)	13 (7.5)
Joint swelling	3 (1.7)	3 (1.7)
Arthropathy	1 (0.6)	-
Epicondylitis	-	1 (0.6)
Joint effusion	1 (0.6)	-
Limb discomfort	-	1 (0.6)
Muscular weakness	1 (0.6)	-
Musculoskeletal discomfort	1 (0.6)	-
Myalgia	-	1 (0.6)
Pain in extremity	1 (0.6)	-
Skin and subcutaneous tissue disorders	1 (0.6)	-
Erythema	1 (0.6)	-

Table 8: Mixed Model Repeated Measures Analysis of WOMAC Pain Subscale Score CFB by Visit –Per Protocol Set

		Actual Result		Change from Baseline		Baseline Change Difference (95% CI)
Visit (week)		**DUROLANE (n=161)**	**5-injection HA (n=158)**	**DUROLANE (n=161)**	**5-injection HA (n=158)**	**DUROLANE - 5-injection HA**
Baseline (Week 0)	Mean(SD)	9.4 (1.98)	9.5 (1.80)	-	-	-
Visit 7 (Week 6)	Mean(SD)	4.6 (3.32)	4.6 (2.93)	-4.9 (3.16)	-5.0 (2.68)	-
	LSM (95% CI)	-	-	-5.02 (-5.46; -4.58)	-5.06 (-5.50; -4.61)	0.04 (-0.58; 0.65)
	p value	-	-	<0.0001	<0.0001	0.91
Visit 8 (Week 10)	Mean(SD)	3.7 (3.19)	3.7 (2.81)	-5.7 (3.03)	-5.8 (2.65)	-
	LSM (95% CI)	-	-	-5.45 (-5.85; -5.05)	-5.49 (-5.89; -5.09)	0.04 (-0.51; 0.59)
	p value	-	-	<0.0001	<0.0001	0.89
Visit 9 (Week 14)	Mean(SD)	3.2 (2.90)	3.4 (2.69)	-6.2 (2.87)	-6.1 (2.59)	-
	LSM (95% CI)	-	-	-5.76 (-6.14; -5.39)	-5.73 (-6.11; -5.36)	-0.03 (-0.54; 0.48)
	p value	-	-	<0.0001	<0.0001	0.91
Visit 10 (Week 18)	Mean(SD)	3.0 (2.88)	3.3 (2.75)	-6.5 (2.79)	-6.2 (2.75)	-
	LSM (95% CI)	-	-	-5.97 (-6.32; -5.61)	-5.87 (-6.23; -5.52)	-0.09 (-0.58; 0.39)
	p value	-	-	<0.0001	<0.0001	0.70
Visit 11 (Week 26)	Mean(SD)	2.8 (2.73)	2.9 (2.68)	-6.6 (2.67)	-6.6 (2.58)	-
	LSM (95% CI)	-	-	-6.15 (-6.49; -5.81)	-6.05 (-6.39; -5.71)	-0.10 (-0.56; 0.37)
	p value	-	-	<0.0001	<0.0001	0.68

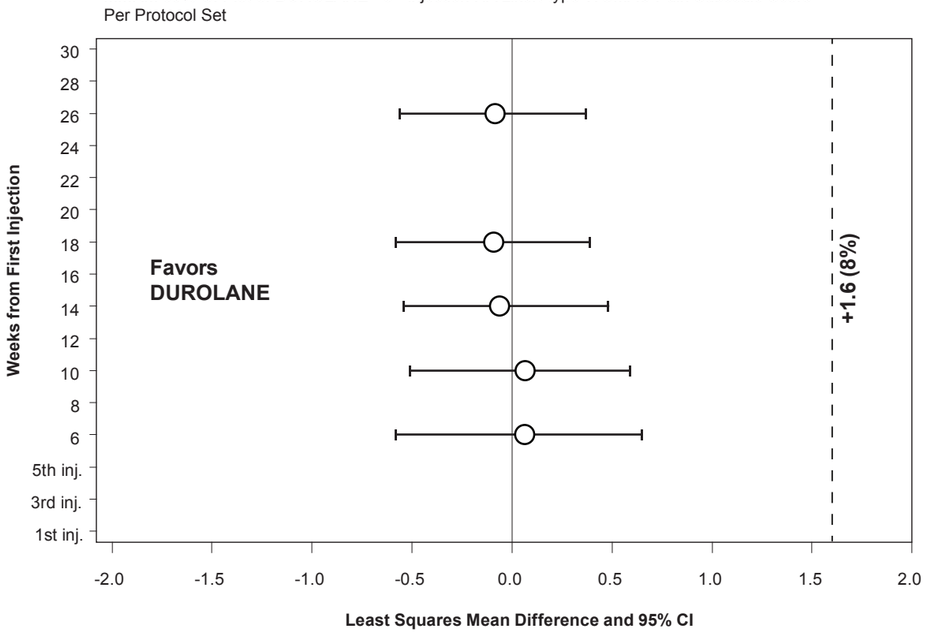
CI = Confidence Interval; SD = Standard Deviation; LSM = Least Squares Mean

Table 9: Results of Stepwise Non-inferiority Analyses of Other Secondary Effectiveness Variables

Secondary Variable (order of importance)	Baseline Change Mean (SD)		LSM (95% CI) (DUROLANE - 5-injection HA)	Non-Inferiority 8% Margins	Conclusion
	DUROLANE	5-injection HA			
WOMAC Physical Function CFB (over 18 weeks)	-12.75 (-13.60; -11.91)	-12.10 (-12.95; -11.26)	-0.65 (-1.81, 0.51)	+5.44	Non-inferior
WOMAC Physical Function CFB (over 26 weeks)	-12.58 (-13.39; -11.77)	-13.16 (-13.97; -12.35)	-0.58 (-1.69, 0.53)	+5.44	Non-inferior
Subject Global Assessment CFB (over 18 weeks)	2.70 (2.48; 2.92)	2.55 (2.33; 2.77)	0.15 (-0.15, 0.45)	-0.8	Non-inferior
Subject Global Assessment CFB (over 26 weeks)	2.81 (2.59; 3.02)	2.67 (2.45; 2.88)	0.14 (-0.16, 0.43)	-0.8	Non-inferior
WOMAC Knee Stiffness CFB (over 18 weeks)	-1.87 (-2.00; -1.73)	-1.73 (-1.87; -1.59)	-0.14 (-0.33, 0.05)	+0.64	Non-inferior
WOMAC Knee Stiffness CFB (over 26 weeks)	-1.95 (-2.08; -1.82)	-1.80 (-1.93; -1.67)	-0.15 (-0.33, 0.03)	+0.64	Non-inferior

CFB = Change From Baseline; CI = Confidence Interval; SD = Standard Deviation; LSM = Least Squares Mean

Figure 1: Mixed Model Repeated Measures (MMRM) 95% CI Plot



Note: confidence interval information is cumulative first Week 6, then Week 6 and 10, etceteras to Week 26.

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DUROLANE PATIENT INFORMATION

Please make sure to read the following important information carefully. This information does not take the place of your doctor's advice. If you do not understand this information or want to know more, ask your doctor.

GLOSSARY

Hyaluronan is a natural substance that is present in very high amounts in joints, skin and eyes. It is a major part of the synovial (cushioning) fluid in your joints and functions as a lubricant and a shock absorber.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are medications used to treat pain. There are many examples of NSAIDs, including (but not limited to) aspirin and ibuprofen (e.g. Advil®, Motrin®, etc.). Some of these drugs are available over-the-counter, while stronger, more potent, versions can be obtained with a doctor's prescription.

Osteoarthritis (OA) is a joint disease that shows itself as a type of arthritis that involves the wearing down of cartilage (the protective layer covering the ends of the bones) caused by loss of quality of the cushioning (synovial) fluid in the joint.

WHAT IS DUROLANE?

DUROLANE is a clear, viscous gel that contains highly purified sodium hyaluronate. Sodium hyaluronate is found in the body, particularly in joint tissue and fluid surrounding the joint. This substance acts as a lubricant and shock absorber in the knee joint.

In joints affected by osteoarthritis, the concentration of sodium hyaluronate and its ability to lubricate and cushion may be reduced. Therefore, injection of sodium hyaluronate directly into the joint may increase lubrication and cushioning, relieving pain during physical activity.

The sodium hyaluronate in DUROLANE is produced by bacterial fermentation. DUROLANE is provided to your doctor as a single syringe containing 3 mL of gel.

WHAT IS DUROLANE USED FOR?

DUROLANE is used to relieve knee pain due to osteoarthritis, improving patient capacity for physical activity. It is used for patients who do not get enough pain relief from conservative therapies, such as exercise or physical therapy.

HOW IS DUROLANE GIVEN?

Your doctor will give you a single injection of DUROLANE (3 mL, 20 mg/mL) into your knee joint.

WHAT ARE THE POSSIBLE SIDE EFFECTS?

Common side effects (also called reactions) that may occur during the use of DUROLANE include pain, joint pain, joint swelling, and joint stiffness at the injection site. The majority of reactions are mild to moderate in nature and do not last long. No treatment-related allergic reactions or acute inflammatory reactions or hypersensitivity to DUROLANE have been reported from the controlled clinical studies.

If any of the above symptoms or signs appear after you are given DUROLANE, or if you are experiencing any other problems, you should call your healthcare professional.

WHAT SIDE EFFECTS WERE OBSERVED IN THE CLINICAL STUDIES?

In the DUROLANE treatment group for a clinical study performed in the People's Republic of China (PRC), the adverse events included injection site pain (2.3%), joint swelling (1.7%), and joint pain (8.6%). These adverse events were comparable to those reported in a control group that was treated with a commercially available 5-injection sodium hyaluronate, and adverse events in the control group included injection site pain (1.1%), joint swelling (1.7%), and joint pain (7.5%). Most of the reactions in both groups were mild to moderate in nature and did not last long.

WHAT ARE THE BENEFITS OF DUROLANE?

Data from a clinical trial showed that a single injection of DUROLANE provided comparable pain relief to patients with osteoarthritis of the knee to the pain relief provided by 5 injections of another commercially available sodium hyaluronate. The patients in the study had been diagnosed with OA of the knee associated with moderate to severe pain, and did not obtain sufficient relief with simple analgesics (e.g. acetaminophen) taken by mouth.

A total of 349 patients in the study were assigned by chance to receive either a single injection treatment of DUROLANE (n=175 patients), or a 5-injection procedure using a commercially available hyaluronate (n=174 patients). Neither the patients nor the doctors evaluating them knew which treatment they received. Patients were observed by their doctor over 6 months. DUROLANE demonstrated a similar safety profile to that of the 5-injection sodium hyaluronate product when injected in the knee.

The pain relieving benefits of DUROLANE were compared with the same measures of a similar 5-injection sodium hyaluronate product that is manufactured by another company. The other product was approved in the US as a 5-injection regimen (treatment) and helped many patients with osteoarthritis. This comparison was used to show that DUROLANE provides no inferior pain relief in a single injection. The main measure of the comparison was how much less pain the subjects had experienced over a 6 month time period.

WHAT OTHER TREATMENTS ARE AVAILABLE FOR OSTEOARTHRITIS?

If you have osteoarthritis, there are a number of approaches available to relieve your symptoms. These include:

Non-drug treatments:

- Avoidance of activities that cause knee pain
- Exercise
- Physical therapy
- Non-drug treatments (e.g. glucosamine, chondroitin)
- Removal of excess fluid from the knee
- Total knee replacement
- Arthroscopic surgery

Drug therapy:

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

ARE THERE ANY REASONS WHY YOU SHOULD NOT RECEIVE DUROLANE?

- You should not be given this product if you have a knee joint infection or skin disease or infection around the area where the injection will be given.
- You should not use this product if you are allergic to sodium hyaluronate products.

THINGS YOU SHOULD KNOW ABOUT DUROLANE

- DUROLANE should only be injected by a doctor or other qualified healthcare professional.
- Tell your healthcare professional if you are allergic to sodium hyaluronate based products.
- As with other injection products, you may need to avoid activities such as jogging, tennis, standing for a long time (more than an hour) or heavy lifting for 48 hours after the injection.
- DUROLANE has not been approved for use in joints other than the knee.
- The safety and efficacy of DUROLANE have not been established in children (21 years of age or younger), pregnant women or nursing mothers.
- The effectiveness of DUROLANE has not been established for more than one course of treatment.

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DUROLANE® es

INFORMACIÓN DE DUROLANE PARA EL PACIENTE

Asegúrese de leer atentamente la siguiente información. Esta información no reemplaza las indicaciones de su médico. Consulte con su médico si no entiende esta información o si quiere obtener más detalles.

GLOSARIO

Hialuronano: sustancia natural que se encuentra en muy altas concentraciones en las articulaciones, la piel y los ojos. Es un componente primordial del líquido sinovial de las articulaciones y funciona como lubricante y amortiguador.

Antiinflamatorios no esteroideos (AINE): medicamentos utilizados para el tratamiento del dolor. Algunos ejemplos de AINE incluyen, entre otros, la aspirina y el ibuprofeno (por ejemplo Advil®, Motrin®, etc.). Algunos de estos medicamentos son de venta libre, aunque sus presentaciones más concentradas pueden adquirirse con prescripción médica.

Osteoartritis (OA): enfermedad de las articulaciones que se manifiesta como un tipo de artritis que supone un desgaste del cartílago (la capa protectora que rodea los extremos de los huesos) y es causada por la pérdida de la calidad de líquido de amortiguación (sinovial) en la articulación.

¿QUÉ ES DUROLANE?

DUROLANE es un gel transparente y viscoso que contiene hialuronato de sodio de alta pureza. El hialuronato de sodio se encuentra en el cuerpo, en especial en el tejido articular y el líquido que rodea la articulación. Esta sustancia actúa como un lubricante y amortiguador en la articulación de la rodilla.

En las articulaciones afectadas por artrosis, es posible que se reduzca la concentración de hialuronato de sodio y su capacidad de lubricación y amortiguación. Por lo tanto, la inyección de hialuronato de sodio directamente en la articulación puede aumentar la lubricación y amortiguación, lo que alivia el dolor al realizar actividad física.

Hialuronato de sodio en DUROLANE se produce mediante fermentación bacteriana. DUROLANE se proporciona a su médico en una jeringa única que contiene 3 mL de gel.

¿PARA QUÉ SE UTILIZA DUROLANE?

DUROLANE se utiliza para aliviar el dolor de rodilla ocasionado por artrosis, lo que mejora la capacidad del paciente para realizar actividad física. Se utiliza en pacientes que no consiguen alivio suficiente a partir de tratamientos conservadores, tales como el ejercicio y la terapia física.

¿CÓMO SE ADMINISTRA DUROLANE?

Su médico le administrará una sola inyección de DUROLANE (3 mL, 20 mg/mL) en la articulación de la rodilla.

¿CUÁLES SON LOS POSIBLES EFECTOS SECUNDARIOS?

Los efectos secundarios más comunes (también llamados reacciones) que pueden ocurrir durante la aplicación de DUROLANE incluyen dolor, dolor articular, hinchazón y rigidez articular en el lugar de la inyección. La mayoría de las reacciones son de naturaleza leve a moderada y no permanecen mucho tiempo. No se informaron reacciones alérgicas relacionadas al tratamiento, ni reacciones inflamatorias agudas ni hipersensibilidad a DUROLANE a partir de los estudios clínicos controlados.

Si alguno de estos síntomas o signos aparece luego de que se le administra DUROLANE, o si presenta algún otro problema, debe llamar a su profesional de la salud de inmediato.

¿QUÉ EFECTOS SECUNDARIOS SE OBSERVARON EN LOS ESTUDIOS CLÍNICOS?

En un estudio clínico a un grupo que realizaba un tratamiento con DUROLANE realizado en la República Popular China, los efectos secundarios incluyeron dolor en el lugar de la inyección (2,3 %), hinchazón articular (1,7 %) y dolor articular (8,6 %). Estos efectos secundarios fueron similares a los que se informaron en un grupo de control al que se administró un tratamiento comercialmente disponible de 5 inyecciones de hialuronato de sodio. Los eventos adversos en el grupo de control incluyeron dolor en el lugar de la inyección (1,1 %), hinchazón articular (1,7 %) y dolor articular (7,5 %). La mayoría de las reacciones en ambos grupos fueron de naturaleza leve a moderada y no permanecieron mucho tiempo.

¿CUÁLES SON LOS BENEFICIOS DE DUROLANE?

Los datos de un ensayo clínico realizado demostraron que una sola inyección de DUROLANE ofrece un alivio del dolor a los pacientes con osteoartritis de rodilla similar al alivio de 5 inyecciones de otro producto con hialuronato de sodio comercialmente disponible. Los pacientes en el estudio habían recibido diagnóstico de OA de rodilla con dolor moderado a intenso; y no obtuvieron el alivio suficiente con analgésicos comunes administrados por vía oral (por ejemplo acetaminofén).

En el estudio, se asignó un total de 349 pacientes al azar para recibir una dosis única de DUROLANE (n=175 pacientes) o el tratamiento comercialmente disponible de 5 inyecciones de hialuronato de sodio (n=174 pacientes). Ni los pacientes ni los médicos que los evaluaban sabían qué tratamiento habían recibido. Se observó a los pacientes por 6 meses. Al inyectarse en la rodilla, DUROLANE demostró un perfil de seguridad similar al del tratamiento de 5 inyecciones de hialuronato de sodio.

Se comparó el alivio del dolor proporcionado por DUROLANE con el de un tratamiento similar de 5 inyecciones de hialuronato de sodio fabricado por otra empresa. Se aprobó el otro producto en EE. UU. como un tratamiento de 5 inyecciones y ayudó a muchos pacientes con osteoartritis. Esta comparación se utilizó para demostrar que DUROLANE suministra el mismo alivio del dolor pero en una sola inyección. La medida principal de la comparación fue cuánto dolor dejaban de experimentar los sujetos durante un período de 6 meses.

¿QUÉ OTROS TRATAMIENTOS EXISTEN PARA LA ARTROSIS?

Si presenta osteoartritis, existen varios métodos disponibles para aliviar los síntomas. Se incluyen los siguientes:

Tratamientos sin medicamentos:

- Eliminación de actividades que produzcan dolor de rodilla
- Ejercicio
- Terapia física
- Tratamientos sin medicamento (por ejemplo, gluco¬samina, condroitina)
- Extracción del líquido extra acumulado en la rodilla
- Reemplazo de rodilla total
- Cirugía artroscópica

Tratamientos con medicamentos:

- Analgésicos, tales como acetaminofén o estupe-facientes
- Medicamentos para disminuir la inflamación (los signos de inflamación son hinchazón, dolor o enrojecimiento), tales como aspirinas, y otros medicamentos antiinflamatorios no esteroides (AINE), como ibuprofeno o naproxeno
- Esteroides que se inyectan directamente en la rodilla

¿HAY ALGÚN MOTIVO POR EL QUE NO DEBERÍA RECIBIR DUROLANE?

- No se debe administrar este producto si tiene una infección en la rodilla, o una enfermedad cutánea o una infección alrededor del área donde se administrará la inyección.
- No se debe administrar este producto si es alérgico a los productos de hialuronato de sodio.

COSAS QUE DEBE SABER ACERCA DE DUROLANE

- Solamente un médico u otro profesional de la salud capacitado debe inyectar DUROLANE.
- Si es alérgico a los productos a base de hialuronato de sodio, comuníqueselo a su profesional de la salud.
- Al igual que con otros productos inyectables, es posible que necesite evitar actividades como trotar, jugar al tenis, o estar parado durante un tiempo prolongado (más de una hora), o levantar objetos pesados durante las 48 horas posteriores a la inyección.
- No se aprobó la administración de DUROLANE en otras articulaciones además de la rodilla.
- No se determinó la seguridad y eficacia de DUROLANE en niños (hasta 21 años de edad), embarazas o madres en lactancia.
- No se determinó la efectividad de DUROLANE por más de un ciclo de tratamiento.

FABRICANTE

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