LABELING

Hyalgan®

(Sodium Hyaluronate)

CAUTION

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

DESCRIPTION

Hyalgan® is a viscous solution consisting of a high molecular weight (500,000–730,000 daltons) fraction of purified natural sodium hyaluronate (Hyalectin®) in buffered physiological sodium chloride, having a pH of 6.8-7.5. The sodium hyaluronate is extracted from rooster combs. Hyaluronic acid is a natural complex sugar of the glycosaminoglycan family and is a long-chain polymer containing repeating disaccharide units of Na-glucuronate-N-acetylglucosamine.

INDICATIONS

Hyalgan® is indicated for the treatment of pain in osteoarthritis (OA) of the knee in patients who have failed to respond adequately to conservative nonpharmacologic therapy, and to simple analgesics, e.g., acetaminophen.

CONTRAINDICATIONS

- Do not administer to patients with known hypersensitivity to hyaluronate preparations.
- Intra-articular injections are contraindicated in cases of present infections or skin diseases in the area of the injection site to reduce the potential for developing septic arthritis.

WARNINGS

- Do not concomitantly use disinfectants containing quaternary ammonium salts for skin preparation because hyaluronic acid can precipitate in their presence.
- Anaphylactoid and allergic reactions have been reported with this product. See Adverse Events Section for more detail.
- Transient increases in inflammation in the injected knee following Hyalgan® injection in some patients with inflammatory arthritis such as rheumatoid arthritis or gouty arthritis have been reported.
- Patients should be carefully examined prior to administration to determine signs of acute inflammation, and the physician should evaluate whether Hyalgan® treatment should be initiated when objective signs of inflammation are present.

PRECAUTIONS

General

- The effectiveness of a single treatment cycle of less than 3 injections has not been established.
- The safety and effectiveness of the use of Hyalgan® in joints other than the knee have not been established.
- The safety and effectiveness of the use of Hyalgan® concomitantly with other intra-articular injectables have not been established.
- Use caution when injecting Hyalgan® into patients who are allergic to avian proteins, feathers, and egg products.
- Strict aseptic administration technique must be followed to avoid infections in the injection site.
- Remove joint effusion, if present, before injecting Hyalgan®.
- **STERILE CONTENTS.** The vial/syringe is intended for single use. The contents of the vial/syringe must be used immediately once the container has been opened. Discard any unused Hyalgan®.
- Do not use Hyalgan® if the package is opened or damaged. Store in the original packaging (protected from light) below 77° F (25° C). DO NOT FREEZE.

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 Hyalgan®.
- 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 48 hours following the intra-articular injection.

Use in Specific Populations

- **Pregnancy:** *Teratogenic Effects*- Reproductive toxicity studies, including multigeneration studies, have been performed in rats and rabbits at doses up to 11 times the anticipated human dose (1.43 mg/kg per treatment cycle) and have revealed no evidence of impaired fertility or harm to the experimental animal fetus due to intra-articular injections of Hyalgan®. Animal reproduction studies are not always predictive of human response. The safety and effectiveness of Hyalgan® have not been established in pregnant women.
- **Nursing Mothers:** It is not known if Hyalgan® is excreted in human milk. The safety and effectiveness of Hyalgan® have not been established in lactating women.
- **Pediatrics:** The safety and effectiveness of Hyalgan® have not been demonstrated in children.

ADVERSE EVENTS

Hyalgan® was investigated in a pivotal clinical investigation conducted in the United States in which there were three arms (164 subjects treated with Hyalgan®; 168 with placebo; and 163 with naproxen) (refer to Table 1). Common adverse events reported for the Hyalgan®-treated subjects were gastrointestinal complaints, injection site pain, knee swelling/effusion, local skin reactions (rash, ecchymosis), pruritus, and headache. Swelling and effusion, local skin reactions (ecchymosis and rash), and headache occurred at equal frequency in the Hyalgan®- and placebo-treated groups. Hyalgan® treated subjects had 48/164 (29%) incidents of gastrointestinal complaints that were not statistically different from the placebo-treated group. A statistically significant difference in the occurrence of pain at the injection site was noted in the Hyalgan®-treated subjects: 38/164 (23%) in comparison to 22/168 (13%) in the placebo-treated subjects ($p = 0.022$). There were 6/164 (4%) premature discontinuations in Hyalgan®-treated subjects due to injection site pain in comparison to 1/168 (<1%) in the placebo-treated subjects. These differences were not statistically significant. Two (2/164, 1.2%) Hyalgan®-treated subjects and 3/168 (1.8%) placebo-treated subjects were reported to have positive bacterial cultures of effusion aspirated from the treated knee. The two Hyalgan®-treated subjects and two of the placebo-treated subjects did not exhibit evidence of infection clinically or subsequently and were not treated with antibiotics. One of the placebo-treated subjects was hospitalized and received presumptive treatment for septic arthritis.

Hyalgan® has been in clinical use in Europe since 1987. Analysis of the adverse events that have been reported with the use of Hyalgan® in Europe reveals that most of the events are related to local symptoms such as pain, swelling/effusion, and warmth or redness at the injection site. Usually such symptoms disappear within a few days by resting the affected joint and applying ice locally. Only sporadically have these events been more severe and longer lasting. Very rare cases of intra-articular infection have been reported. Strict aseptic technique must be followed in administering Hyalgan®. Systemic allergic reactions rarely have been recorded. Isolated cases of an anaphylactic or anaphylactic-like reaction have been reported in post-marketing experience and they all resolved. Allergic-type signs and symptoms such as rash, pruritus, and urticaria also are very rare. A few cases of fever were reported. In some instances, they were associated with local reactions, in other cases, no association other than temporal was found with the use of the product.

Adverse experience data from the literature contain no evidence of increased risk relating to retreatment with Hyalgan®. The frequency and severity of adverse events occurring during repeat treatment cycles did not increase over that reported for a single treatment cycle. (Carrabba et al., 1995; Carrabba et al., 1991; Kotz and Kolarz, 1999; Scali, 1995).

CLINICAL STUDY

The use of Hyalgan® as a treatment for pain in OA of the knee was investigated in a multicenter clinical trial conducted in the United States.

Study Design

This study was a double-masked, placebo and naproxen-controlled, multicenter prospective clinical trial with three treatment arms, as summarized in Table 2. A total of 495 subjects with moderate to severe pain was randomized (at baseline evaluation) into three treatment groups in a ratio of 1:1:1 Hyalgan®, placebo, or naproxen.

TABLE 2 STUDY DESIGN

Routes of Administration	Hyalgan®	Placebo	Naproxen
s.c. i.a.* p.o./b.i.d. p.o./p.r.n. (not to exceed 4 grams/day)	Lidocaine (1%) Hyalgan® (20 mg/2 mL) Placebo for naproxen capsules Acetaminophen	Lidocaine (1%) Phosphate-Buffered Saline (2 mL) Placebo for naproxen capsules Acetaminophen	Lidocaine (1%) none Naproxen capsules (500 mg) Acetaminophen

Legend: s.c. = subcutaneous; i.a. = intra-articular; p.o. = by mouth; b.i.d. = twice a day; p.r.n. = as needed
* Synovial fluid was aspirated (when present) in the Hyalgan® and placebo groups.

Patient Population and Demographics

The demographics of trial participants were comparable across treatment groups with regard to age, sex, race, height, weight, history of osteoarthritis, prior use of NSAIDs, prior physical therapy, and use of assistive devices (refer to Table 3).

Evaluation Schedule

After meeting initial screening requirements NSAID therapy was discontinued. After 2 weeks, all subjects returned for baseline evaluations. The baseline evaluation included assessment of three primary effectiveness criteria; measurement of pain during a 50-foot walk test using a 100 mm Visual Analog Scale (VAS), a categorical assessment (0 = none to 5 = disabled) of pain, as assessed by a masked evaluator, during the 48 hours preceding the visit, and a categorical assessment (0 = none to 5 = disabled) of pain, as assessed by the subject, during the 48 hours preceding the visit.

All subjects who completed the NSAID washout period and met all entry requirements received their first injection after randomization.
All subjects received subcutaneous lidocaine injections.
Intra-articular injections (Hyalgan®, placebo) were administered weekly for a total of 5 injections (Weeks 0–4). The naproxen group received 500 mg of naproxen to be taken b.i.d. for 26 weeks.
Subsequent visits and evaluations took place at Weeks 5, 9, 12, 16, 21, and 26. Safety and effectiveness criteria were assessed and recorded at these time periods.

Clinical Results

For this trial, overall success for effectiveness was defined as meeting all four of the success criteria listed in Table 4 using scores from week 26. The criteria were met (refer to Tables 4 through 8).

Additional Analyses

a. An analysis of study completers was performed as follows: Success was defined as 1) achieving a 20 mm decrease in the VAS for the 50-foot walk test by Week 5, and 2) maintaining this improvement through Week 26. In this analysis greater proportions of Hyalgan®-treated subjects (59/105, 56%) than either placebo (47/115, 41%) or naproxen-treated subjects (51/113, 45%) were successful under this definition. The Hyalgan®-placebo comparison was statistically significant ($p=0.031$, Fisher's Exact Test). Since patients were not followed beyond Week 26, it is unknown how long pain relief continued. There are reports in the literature of some patients experiencing benefit beyond 26 weeks.

b. Categorical Assessment of Pain - Subjects: A longitudinal analysis of categorical assessment of pain by the subject, which analyzed the percentage of subjects who attained success revealed that a significantly higher percentage of Hyalgan®-treated subjects as compared to the placebo-treated subjects (55/105, 52% vs 43/115, 37%, $p = 0.030$, Fisher's Exact Test) achieved success (an improvement of greater than or equal to one point on the five-point scale) and maintained this success from Week 5 until Week 26.

Supplementary Clinical Information

Three randomized, controlled clinical investigations were performed that provide information about a three-injection treatment course of Hyalgan®. In all of the studies the patients were followed for 60 days.
Two studies provided a comparison to placebo. One of the placebo-controlled studies evaluated two treatment doses of Hyalgan®, 20 mg/2 ml and 40 mg/2 ml. The 20 mg/2 ml treatment arm included 19 knees, the 40 mg/2 ml included 20 knees, and the placebo arm included 18 knees. The other placebo study included 20 knees in the treatment group and 18 knees in the placebo-treatment group. The third study provided a comparison between patients treated with three weekly injections of Hyalgan® followed by 2 weekly treatments with arthrocentesis with patients treated with arthrocentesis for five weeks, and arthrocentesis and placebo injections for five weeks. Additional arms of this study assessed additional treatment regimens. Statistical evaluation of the data was performed at day 60. In this study, only patients considered to be success were followed beyond day 60. These patients were followed for 180 days, however, due to the number of dropouts, statistical evaluation was not performed on data gathered at time points beyond day 60. The results of these investigations reported that the three-injection Hyalgan® treated patients experienced pain relief beginning at day 21 and continuing throughout the remaining 60-day observation period.

Safety

In order for the product to be considered safe, the incidence of severe swelling and pain consequent to intra-articular injection should be less than 5%. This criterion was met as indicated in Table 1. See the Adverse Events Section.

DETAILED DEVICE DESCRIPTION

Each vial or syringe contains:

Sodium Hyaluronate	20.0 mg
Sodium chloride	17.0 mg
Monobasic sodium phosphate • $2H_2O$	0.1 mg
Dibasic sodium phosphate • $12H_2O$	1.2 mg
Water for injection	q.s.* to 2.0 mL

*q.s. = up to

HOW SUPPLIED

Hyalgan® is supplied as a sterile, non-pyrogenic solution in 2 mL vials or 2 mL pre-filled syringes.

DIRECTIONS FOR USE

Hyalgan® is administered by intra-articular injection. A treatment cycle consists of five injections given at weekly intervals. Some patients may experience benefit with three injections given at weekly intervals. This has been noted in studies reported in the literature in which patients treated with three injections were followed for 60 days.
Precaution: Do not use Hyalgan® if the package is opened or damaged. Store in the original packaging (protected from light) below 77° F (25° C). DO NOT FREEZE.
Precaution: Strict aseptic administration technique must be followed.
Warning: Do not concomitantly use disinfectants containing quaternary ammonium salts for skin preparation because hyaluronic acid can precipitate in their presence.
Inject subcutaneous lidocaine or similar local anesthetic prior to injection of Hyalgan®.
Precaution: Remove joint effusion, if present, before injection of Hyalgan®.
Do not use the same syringe for removing joint effusion and for injecting Hyalgan®.
Take care to remove the tip cap of the syringe and needle aseptically.
Inject Hyalgan® into the joint through a 20-gauge needle.
Precaution: The vial/syringe is intended for single use. The contents of the vial must be used immediately once the container has been opened. Discard any unused Hyalgan®. Inject the full 2 mL in one knee only. If treatment is bilateral, a separate vial should be used for each knee.

MANUFACTURED BY

Fidia Farmaceutici S.p.A.
Via Ponte della Fabbrica 3/A - 35031 Abano Terme, Padua (PD), Italy

MANUFACTURED FOR

Fidia Pharma USA Inc.
Parsippany, NJ 07054

REFERENCES

1. M. Carrabba et al., 1991 Hyaluronic acid sodium salt (Hyalgan®) in the treatment of patients with osteoarthritis of the knee: a controlled trial versus Orgotein, Final Report, April 1991. Data on file.
2. M. Carrabba et al., 1995. Effectiveness and safety of 1, 3 and 5 injections of 20 mg/2 ml Hyalgan® in comparison with a placebo and with arthrocentesis only, in the treatment of knee osteoarthritis. European Journal of Rheumatology and Inflammation 15:25-31.
3. M. Dougados et al., 1993. High molecular weight sodium hyaluronate (hyalectin) in osteoarthritis of the knee: a one-year placebo-controlled trial. Osteoarthritis and Cartilage 1:97-103.
4. R. Kotz and G. Kolarz, 1997 published as R. Kotz and G. Kolarz, 1999. Intra-articular hyaluronic acid: duration of effect and results of repeated treatment cycles. The American Journal of Orthopedics, 28:5-7.
5. G. Leardini et al., 1987. Intra-articular sodium hyaluronate (Hyalgan®) in gonarthrosis. Clinical Trials Journal 24(4):341-350.
6. J.J. Scali, 1995. Intra-articular hyaluronic acid in the treatment of osteoarthritis of the knee: a long term study 15(1):57-62.

Revised May 2014

(Sodium Hyaluronate)
Hyalgan®
LABELING

LABELING

Hyalgan®

(Sodium Hyaluronate)

6840734

TABLE 1

Incidence[1] of Adverse Events Occurring in More than 5% of All Subjects

Adverse Event	Hyalgan® N = 164	Placebo N = 168
Gastrointestinal Complaints[2]	48 (29%)	59 (36%)
Injection site pain[3]	38 (23%)[4]	22 (13%)
Headache	30 (18%)	29 (17%)
Local skin[5]	23 (14%)	17 (10%)
Local joint pain and swelling[6]	21 (13%)	22 (13%)
Pruritus (local)	12 (7%)	7 (4%)

Notes: [1]Number and % of subjects
[2]Severe in 4 Hyalgan®-treated subjects and 4 placebo-treated subjects
[3]Severe in 5 Hyalgan®-treated subjects and 2 placebo-treated subjects
[4]Statistically significant (p=0.02)
[5]Includes ecchymosis and rash
[6]Severe in 2 Hyalgan®-treated subjects (1.2%) and 1 placebo-treated subject

TABLE 3

Demographic Characteristics of all randomized subjects

DEMOGRAPHIC VARIABLE	TREATMENT			
	Hyalgan® N = 164	Placebo N = 168	Naproxen N = 163	TOTAL N = 495
AGE (years):				
Mean	63.5	64.3	63.2	63.7
SD	10.1	10.0	9.2	9.8
Range	41-90	44-85	40-80	40-90
Gender [N (%)]:				
Female	99 (60.3)	91 (54.1)	99 (60.7)	289 (58.4)
Male	65 (39.6)	77 (45.8)	64 (39.3)	206 (41.6)
Race [N (%)]:				
Caucasian	137 (83.6)	135 (80.4)	133 (81.6)	405 (81.8)
Black	23 (14.0)	32 (19.0)	25 (15.3)	80 (16.2)
Other	4 (4.2)	1 (1.0)	5 (3.1)	10 (2.0)
Height (cm):				
Mean	167.8	168.6	167.6	168.0
SD	8.8	10.7	11.9	10.5
Range	145-190	142-193	102-198	102-198
Weight (kg):				
Mean	88.4	88.1	89.7	88.7
SD	18.0	18.2	18.4	18.2
Range	46-139	49-170	45-150	45-170
NSAIDs Use (N, %)	107 (65.2)	117 (69.6)	113 (69.3)	337 (68.1)
Use of Assistive Devices (N, %)	35 (21.3)	34 (20.2)	32 (19.6)	101 (20.4)
Physical Therapy (N, %)	20 (12.2)	17 (10.1)	25 (15.3)	62 (12.5)

Legend: cm = centimeters; kg = kilograms; SD = standard deviation

TABLE 4

Clinical Results

Evaluation	Success Criteria	Results
100 mm VAS for pain during 50 foot walk.	A statistically significant (alpha = 0.05) reduction on mean VAS for Hyalgan® when compared to placebo at Week 26. This difference was also to exceed one fourth of the Standard Deviation of the mean change from baseline.	At Week 26, the difference between the Hyalgan®-treated group and the placebo-treated group adjusted means was 8.85 mm (p = 0.0043), which is a difference of approximately one-third of a standard deviation (Table 5).
Masked Evaluator Categorical Assessment of subject pain (0=none to 5=disabled) during the 48 hours preceding visits.	The number of Hyalgan®-treated subjects showing improvement at Week 26 was to be concordant with the VAS results, however, not required to be independently statistically significant.	At Week 26 the masked evaluator's categorical assessment of pain indicated that the Hyalgan®-treated subjects experienced less pain than the placebo-treated subjects (Table 6).
Subjects' Categorical Assessment of pain (0=none to 5=disabled) during the 48 hours preceding visits.	The number of Hyalgan®-treated subjects showing improvement at Week 26 was to be concordant with the VAS results; however, not required to be independently statistically significant.	At Week 26 the subjects' categorical assessment of pain indicated that the Hyalgan®-treated subjects experienced less pain than the placebo-treated subjects (Table 7).
Magnitude of the observed effect for Hyalgan® versus placebo on both the VAS and the categorical pain assessments.	At Week 26 the magnitude of the observed effect for Hyalgan® versus placebo on both the VAS and the categorical pain assessments were to be at least 50% of those observed for the naproxen group.	The improvement in pain on the VAS exhibited by the Hyalgan®-treated group relative to the placebo-treated group were at least 50% of the benefits exhibited by the naproxen-treated group relative to the placebo-treated group. The results of the categorical assessments by the masked evaluator and the subject indicated that improvement of the Hyalgan®-treated group relative to the placebo-treated group was at least 50% of the benefits exhibited by the naproxen-treated group relative to the placebo-treated group (Table 8).

TABLE 5

ANCOVA of 50-Foot Walk Test (mm) VAS by Week for all Completed Subjects

	Week							
	3	4	5	9	12	16	21	26
Adjusted Means Hyalgan®	27.23	21.54	19.29	20.04	20.26	20.83	18.44	17.88
Placebo	32.35	28.57	25.67	24.28	26.66	25.44	24.77	26.73
Hyalgan® versus Placebo	5.13	7.03	6.39	4.24	6.40	4.61	6.33	8.846
p-value	0.06	0.01	0.01	0.1	0.03	0.1	0.02	0.004

TABLE 6

Masked Evaluators' Categorical Assessments of Pain for Completed Subjects in Prior 48 Hours: Level of Pain by Treatment Group at Baseline and Week 26

	NUMBER (%) OF SUBJECTS IN CATEGORY					
	Hyalgan®		Placebo		Naproxen	
	Baseline	Week 26	Baseline	Week 26	Baseline	Week 26
None (0)	0 (0.0)	27 (25.7)	0 (0.0)	15 (13.0)	0 (0.0)	17 (15.0)
Slight (1)	1 (1.0)	23 (21.9)	0 (0.0)	27 (23.5)	0(0.0)	32 (28.3)
Mild (2)	2 (1.9)	24 (22.9)	2 (1.7)	29 (25.2)	2 (1.8)	27 (23.9)
Moderate (3)	69 (65.7)	26 (24.8)	85 (73.9)	34 (29.6)	79 (70.5)	28 (24.8)
Marked (4)	33 (31.4)	5 (4.8)	28 (24.3)	10 (8.7)	31 (27.7)	9 (8.0)
TOTAL	105 (100)	105 (100)	115 (100)	115 (100)	112* (100)	113 (100)

*One Naproxen treated subject was missing a Baseline assessment.

TABLE 7

Subjects' Categorical Assessments of Pain for Completed Subjects in Prior 48 Hours: Level of Pain by Treatment Group at Baseline and Week 26

	NUMBER (%) OF SUBJECTS IN CATEGORY					
	Hyalgan®		Placebo		Naproxen	
	Baseline	Week 26	Baseline	Week 26	Baseline	Week 26
None (0)	1 (1.0)	23 (21.9)	0 (0.0)	14 (12.2)	0 (0.0)	13 (11.5)
Slight (1)	2 (1.9)	27 (25.7)	0 (0.0)	24 (20.9)	1 (0.9)	31 (27.4)
Mild (2)	6 (5.7)	19 (18.1)	8 (7.0)	24 (20.9)	7 (6.2)	26 (23.0)
Moderate (3)	62 (59.0)	26 (24.8)	78 (67.8)	40 (34.8)	72 (63.7)	31 (27.4)
Marked (4)	34 (32.4)	10 (9.5)	29 (25.2)	13 (11.3)	33 (29.2)	12 (10.6)
TOTAL	105 (100)	105 (100)	115 (100)	115 (100)	113 (100)	113 (100)

TABLE 8

Hyalgan® Effect as a Percentage of the Naproxen-Placebo Difference

Assessment	Hyalgan® (HYL)	Placebo (PLA)	Naproxen (NAP)	HYL-PLA	NAP-HYL	NAP-PLA	(HYL-PLA) % of (NAP-PLA)
VAS for 50 foot Walk Baseline Adjusted Mean Effect Sizes From ANCOVA				-8.85 mm on a 100 mm VAS	4.12 mm on a 100 mm VAS	-4.73* mm on a 100 mm VAS	187%
% of Subjects Improved by Masked Evaluators	78.1	69.6	73.2	8.5	-4.9	3.6	236%
% of Subjects Improved by Subjects	73.3	62.6	67.3	10.7	-6.0	4.7	228%

*Imputed as (NAP-HYL)+(HYL-PLA).
Note that Effectiveness Success Criterion D is satisfied since ((HYL-PLA) % of (NAP-PLA))>50% for all three of the above pain assessments.