TRILURON™

(Sodium Hyaluronate)

CAUTION

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

DESCRIPTION

TRILURON™ is a viscous solution consisting of a high molecular weight (500,000–730,000 daltons) fraction of purified 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

TRILURON™ 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 past and 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 TRILURON™ 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 TRILURON™ 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 TRILURON™ in joints other than the knee have not been established.

- The safety and effectiveness of the use of TRILURON™ concomitantly with other intra-articular injectables have not been established.

- Use caution when injecting TRILURON™ into patients who are allergic to avian proteins, feathers, and egg products.

- Strict aseptic injection technique must be followed to avoid infections in the injection site.

- Remove joint effusion, if present, before injecting TRILURON™.

- **STERILE CONTENTS**. The vial and syringe are intended for single use. The contents must be used immediately once the syringe blister or the vial's seal has been opened. Discard any unused TRILURON™.

- Do not use TRILURON™ 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 TRILURON™.

- 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 TRILURON™. Animal reproduction studies are not always predictive of human response. The safety and effectiveness of TRILURON™ have not been established in pregnant women.

- **Nursing Mothers**: It is not known if TRILURON™ is excreted in human milk. The safety and effectiveness of TRILURON™ have not been established in lactating women.

- **Pediatrics:** The safety and effectiveness of TRILURON™ have not been demonstrated in children.

ADVERSE EVENTS

The sodium hyaluronate formulation for TRILURON™ has been in clinical use in Europe since 1987. In the USA, this same formulation was approved in PMA P950027 for five weekly injections of 20mg of sodium hyaluronate per 2.0mL. The only difference between TRILURON™ and the previously approved formulation is the number of weekly injections. TRILURON™ consists of three weekly injections of 20mg/2.0mL of sodium hyaluronate instead of five. Therefore, the clinical studies from P950027 that established a reasonable assurance of safety of 5 injections of Hyalgan are also applicable to TRILURON™.

The US pivotal clinical study for P950027 provided evidence of reasonable assurance of safety of 5 weekly injections as compared to two controls. The three arms included: 1) 164

subjects receiving 5 weekly injections of 20mg/2.0mL of sodium hyaluronate (referred to as the HA-treated group); 2) 168 subjects receiving 5 weekly injections of 2mL of phosphate-buffered saline (placebo-treated group); and 3) 163 subjects received 5 weekly sham injections and were provided 500mg naproxen capsules (naproxen group.) All patients had a 1% lidocaine injection prior to the treatment or sham injection and all received acetaminophen to take as needed. The HA- and placebo-treated groups received placebo for the naproxen capsules.

Common adverse events reported for the HA-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 HA-and placebo-treated groups. HA-treated subjects had 48/164 (29%) incidents of gastrointestinal complaints, which was 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 HA-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 HA-treated subjects due to injection site pain in comparison to 1/168 (<1%) in the placebo-treated subjects. This difference was not statistically significant.

Two (2/164, 1.2%) HA-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 HA-treated subjects and two of the placebo-treated subjects did not exhibit clinical evidence of infection initially or subsequently and were not treated with antibiotics. One of the placebo-treated subjects was hospitalized and received presumptive treatment for septic arthritis.

For the product to be considered safe, the protocol specified that 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.

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 & swelling[6]	21 (13%)	22 (13%)
Pruritus (local)	12 (7%)	7 (4%)

Note: [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]Included ecchymosis and rash
[6]Severe in 2 Hyalgan®-treated subjects (1.2%) and 1 placebo-treated subject

Additionally, the safety data on TRILURON™ reported by Berenbaum et al.[1] is provided as supporting evidence of the safety of TRILURON™ in the CLINICAL STUDY section.

Supplemental Post-Market Reports

An analysis of the adverse events that have been reported with the use of 5 injection treatment regimen in Europe was provided as additional safety information in P950027. This analysis revealed that most of the events were 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 the HA injection. 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, the fevers were associated with local reactions, and 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 this formulation of sodium hyaluronate. 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[2]; Kotz and Kolarz, 1999[3]; Scali, 1995[4]).

CLINICAL STUDY

The primary evidence of effectiveness for TRILURON™ is provided by a study that is a retrospective analysis of data prospectively collected from two randomized, controlled trials to determine the effectiveness of TRILURON™ (investigational device) compared to Hyalgan (control device). The investigational and control devices (TRILURON™ and Hyalgan, respectively) have the identical chemical formulation and differ only in that a lower dose is injected (3 weekly injections for TRILURON™ compared to 5 weekly injections of Hyalgan). The clinical studies used to provide evidence of the reasonable assurance of the safety of the Hyalgan in P950027[5] are directly applicable to TRILURON™ and thus, the safety of TRILURON™ has already been established.

The study uses the data on the change from baseline in WOMAC Pain after 26 weeks from the Hyalgan treatment arm in the Hyalgan PMA study as a historical control to compare to the data from the TRILURON™ treatment arm of the Berenbaum study. The Berenbaum study includes data for 209 intent-to-treat (ITT) subjects that received the TRILURON™ product and 217 ITT subjects that received another 3 injection HA device. The primary endpoint in the Berenbaum study is the change from baseline at week 26 in WOMAC Pain score, which was also collected as a secondary effectiveness endpoint in the Hyalgan PMA study with data for 105 subjects available at 26 weeks (from n=164 intent-to-treat patients). Therefore, this statistical analysis includes the Hyalgan subjects from the Hyalgan PMA study as a historical control to compare to the results from the Berenbaum study.

Comparisons of study inclusion/exclusion criteria and baseline characteristics between the two groups were performed. These comparisons establish evidence of comparable patient populations. Key patient selection criteria include those shown in Table 2. This table is not exhaustive but includes all the subject selection criteria reported in the Berenbaum study as well as the related criteria from the Hyalgan PMA study.

Table 2 – Key Subject Inclusion/Exclusion Criteria

Criteria	Berenbaum Study	Hyalgan PMA Study
Age	50-80 years	40 years or older
Primary Diagnosis	Knee Osteoarthritis per American College of Rheumatology criteria	Knee Osteoarthritis per American College of Rheumatology criteria
Disease History	History of symptoms for at least 6 months and insufficient/failed response to analgesics and/or regular non-steroidal anti-inflammatory drugs (NSAID), or were intolerant to regular NSAID or weak opioids.	History of symptoms compatible with OA for at least 1 year. And failure to adequately respond to nonpharmacologic care and to simple analgesics, i.e. acetaminophen

Criteria	Berenbaum Study	Hyalgan PMA Study
Current Symptoms	Global knee pain of 40 mm or greater on a 100 mm visual analogue scale (VAS), Western Ontario and McMaster Universities (WOMAC) pain subscale score of 25 or greater on the 0–100 normalized scale and Lequesne index of 4 or greater.	Knee pain on more than half of the days during the preceding month, a minimum of 20mm on at least one of the 5 items in the WOMAC pain subscale and have "moderate" or "marked" pain as assessed by the masked observer.
Contralateral Knee Symptoms	Radiological evidence of bilateral knee osteoarthritis was accepted if global pain VAS in the contralateral knee was less than 30 mm.	Bilateral OA is accepted; in the case of bilateral OA, the knee with the greater level of pain per the 50-foot walk test was identified for treatment.
Kellgren-Lawrence (KL) Grade	II or III	II or III
Exclusions	Isolated/predominantly patellofemoral symptomatic osteoarthritis, secondary knee osteoarthritis, symptomatic hip osteoarthritis homolateral to the target knee, inflammatory or other rheumatic diseases, clinical joint effusion, excessive (≥8°) varus or valgus knee deformity.	Secondary OA or other inflammatory joint disease, acute flare of pseudogout within the past 3 months, joint infection, chronic and active fibromyalgia that would interfere with the evaluation of the patient, gout, intra-articular neoplasm, axial deviation of the lower limbs > 25 degrees in valgus or varus, symptomatic OA of hip or knee that interferes with functional assessment of study knee, clinically significant ML instability, osteonecrosis of either knee that interferes with assessment of the knee.

As key inclusion/exclusion criteria are similar for the two studies, comparable groups are expected. To verify, baseline information will be compared for the two groups including age, gender, body mass index (BMI), percent of subjects in each KL Grade, and WOMAC Pain Subscale at baseline.

The primary effectiveness endpoint is the difference between the investigational and control groups in the mean change from baseline at 26 weeks in WOMAC Pain scores.

As shown in Table 3, the TRILURON™ and Hyalgan populations are similar with regard to demographic and baseline characteristics.

Table 3: Demographics and Baseline Characteristics

Variable		TRILURON™ (Berenbaum Study) (N=209)	Hyalgan (Hyalgan PMA Study) (N=164)
Gender N (%)	Female	134 (64.1)	99 (60.3)
	Male	75 (35.9)	65 (39.6)
Race N (%)	Caucasian	NA	137 (83.6)
	Black	NA	23 (14.0)

Variable		TRILURON™ (Berenbaum Study) (N=209)	Hyalgan (Hyalgan PMA Study) (N=164)
	Other	NA	4 (2.4)
KL Grade N (%)	Grade II	113 (54.1)	56 (34.6)
	Grade III	96 (45.9)	106 (65.4)
BMI (kg/m2)	Mean (SD) (Min, Max) N	27.7 (3.1) (--) N=209	31.42 (6.3) (18.6,57.1) N= 164
Age	Mean (SD) (Min, Max) N	66.1 (8.1) (--) N=209	63.5 (10.1) (41,90) N=164
Preoperative WOMAC Pain	Mean (SD) (Min, Max) N	48.8 (14.9) (--) N=209	48.61 (19.9) (7.8,98.4) N=164

Primary Effectiveness Evaluation

The primary evidence of effectiveness is difference between the mean WOMAC Pain change from baseline at 6 months in the ITT population. Missing data were replaced using the baseline observation carried forward imputation method. This "worst case" method imputes a WOMAC Pain change from baseline of 0 at 26 weeks for each subject with missing data. As shown in Table 4, the mean WOMAC Pain change from baseline at 26 weeks post-first injection were -18.4 and -14.9 in the TRILURON™ and Hyalgan groups, respectively. The difference between the means was -3.545 and the upper limit of the one-sided 95% CI (0.2403) was less than the upper limit of 9. Thus, TRILURON™ is non-inferior to Hyalgan.

Table 4: WOMAC Pain Change from Baseline at 26 Weeks Primary Effectiveness Evaluation (Baseline Observation Carried Forward)

Device	N	Mean WOMAC Pain Change	Std Dev.	Diff btw Means (TRILURON™ - Hyalgan)	Upper Limit of one-sided 95% CI	Non-inferiority (i.e., upper limit <=9)?
TRILURON™	209	-18.4	21.54	-3.545	0.2403	Yes
Hyalgan	164	-14.9	22.56			

Sensitivity Analyses

For the primary endpoint analysis, 59 subjects in the Hyalgan group and 37 in the TRILURON™ group were missing data. As patient level data for the TRILURON™ group were not available, it was not possible to perform analyses using other missing data imputation methods. However, last observation carried forward, completers, multiple imputation and tipping point analyses were performed to assess the effect of missing data in the Hyalgan group on the primary endpoint. These results were compared against the "worst case" baseline-carried-forward imputation for TRILURON™. The sensitivity analyses support the robustness of the non-inferiority finding of the primary endpoint.

Secondary Effectiveness Evaluations

Secondary effectiveness evaluations of TRILURON™ are reported in the Berenbaum study. Improvement over baseline at 26 weeks was demonstrated in the WOMAC Function, Stiffness and Total scores, VAS Pain, Lequesne Index, ICOAP Total, Constant and Intermittent scores, and VAS Patient Global. More than 50% of the TRILURON™ subjects were OARSI/OMERACT responders and achieved the minimum clinically important improvement (MCII) Pain and Function, and more than 40% achieved the patient acceptable symptom state (PASS) Pain, Function and Patient Global, and the MCII Patient Global.

Supporting Evidence of Safety
The safety data on TRILURON™ reported in the Berenbaum study is provided as supporting evidence of the safety of the TRILURON™. The Berenbaum study is a randomized, double-blind, noninferiority trial comparing Hyalgan 3-injection (same chemical formulation as TRILURON™) to another 3-injection hyaluronic acid (Control) in subjects with knee OA. The safety population consisted of 213 subjects treated with TRILURON™ and 223 subjects treated with the control.

The number of subjects with any adverse events was 75 (35.2%) in the TRILURON™ group, which is very similar to the 74 (33.2%) reported in the control group. Most of adverse events were unrelated to the treatment. Back pain was the only AE reported with greater than 3% incidence. Adverse events leading to study discontinuation were reported in 4 (1.9%) in the TRILURON™ group and in 3 (1.3%) in the control group. Local adverse events were reported in 8 (3.8%) subjects in the TRILURON™ group and in 4 (1.8%) in the control group.

As shown in **Table 5**, the local adverse events reported for the TRILURON™ group were joint effusion/swelling (4 subjects, 1.9%), joint pain (2 subjects, 0.9%), injection site hematoma (2 subjects, 0.9%) and injection site warmth (1 subject, 0.5%). The local adverse events reported for the control group were joint effusion/swelling (1 subject, 0.4%) and joint pain (3 subjects, 1.4%). Usually, local adverse events are transient and disappear spontaneously within a few days of resting the affected joint and/or applying ice locally.

Table 5: Local Adverse Events

Local Adverse Event	TRILURON™ #Subjects/All Subjects (%)	Control #Subjects/All Subjects (%)	p-value
Joint effusion/swelling	4/213 (1.9%)	1/223 (0.4%)	
Joint pain	2/213 (0.9%)	3/223 (1.4%)	
Injection site hematoma	2/213 (0.9%)	0 (0%)	
Injection site warmth	1/213 (0.5%)	0 (0%)	
Total	8/213 (3.8%)	4/223 (1.8%)	0.17

The adverse events leading to study discontinuation for TRILURON™ were 4 reports (1.9%), 1 of each of the following: worsening of knee OA, post-traumatic meniscal lesion, ischemic stroke and angiosarcoma with pleural effusion. The adverse events leading to study discontinuation for the control group were 2 reports (0.9%) of worsening of knee OA (one of which was considered possibly related to the treatment) and 1 report (0.4%) of metastatic pulmonary cancer.

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

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

DIRECTIONS FOR USE

TRILURON is administered by intra-articular injection. A treatment cycle consists of three injections given at weekly intervals. Subcutaneous lidocaine or similar local anesthetic may be recommended prior to injection of TRILURON™.

Precaution: Do not use TRILURON™ 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.

Precaution: Remove joint effusion, if present, before injection of TRILURON™.

Do not use the same syringe for removing joint effusion and for injecting TRILURON™.

Take care to remove the tip cap of the syringe and needle aseptically.

Inject TRILURON™ into the joint through a 20-gauge needle.

Precaution: The vial/syringe is intended for single use. The contents must be used immediately once the container has been opened. Discard any unused TRILURON™. Inject the full 2 mL in one knee only. If treatment is bilateral, a separate vial/syringe should be used for each knee.

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REFERENCES

1. Berenbaum, F et al., 2012. A randomised, double-blind, controlled trial comparing two intra-articular hyaluronic acid preparations differing by their molecular weight in symptomatic knee osteoarthritis. Annals of the rheumatic diseases. 71(9), 1454-1460.

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(1):25-31.

3. 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.

4. J.J. Scali, 1995. Intra-articular hyaluronic acid in the treatment of osteoarthritis of the knee: a long term study. European Journal of Rheumatology and Inflammation. 15(1):57-62.

5. Summary of Safety and Effectiveness (SSED) for P950027. - https://www.accessdata.fda.gov/cdrh_docs/pdf/P950027A.pdf

Revised March 2019
Ref. XXXXXX