GenVisc® 850

(sodium hyaluronate)

Full Prescribing Information

CAUTION

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

DESCRIPTION

GenVisc 850[1] is a sterile, viscoelastic non-pyrogenic solution of purified, high molecular weight sodium hyaluronate (average of 850,000 daltons and a range of 620,000 – 1,170,000 daltons) having a pH of 6.8-7.8. Each 2.5 mL of GenVisc 850 contains 10mg/mL of sodium hyaluronate dissolved in a physiological saline (1.0% solution). The sodium hyaluronate is derived from bacterial fermentation. Sodium hyaluronate is a poly-saccharide containing repeating disaccharide units of glucuronic acid and N-acetylglucosamine.

INDICATIONS AND USAGE

GenVisc 850 is indicated for the treatment of pain in osteoarthritis (OA) of the knee in patients who have failed to respond adequately to conservative non-pharmacologic therapy and simple analgesics, e.g., acetaminophen.

CONTRAINDICATIONS

- Do not administer to patients with known hypersensitivity (allergy) to sodium hyaluronate preparations.
- Do not inject this product in the knees of patients with infections or skin diseases in the area of the injection site.

WARNINGS

- Do not concomitantly use disinfectants containing quaternary ammonium salts for skin preparation because sodium hyaluronate can precipitate in their presence.

PRECAUTIONS

- Remove joint effusion, if present, before injecting GenVisc 850.
- Do not use GenVisc 850 if the package is opened or damaged. Store in the original packaging (protected from light) below 86°F (30°C). DO NOT FREEZE. Do not use after expiration date indicated on package. The shelf life of GenVisc 850 is 36 months.
- The effectiveness of a single treatment cycle of less than 3 injections has not been established.
- The effectiveness of repeat treatment cycles of GenVisc 850 has not been established.
- Strict aseptic administration technique must be followed to avoid infections in the injection site.
- The safety and effectiveness of the use of GenVisc 850 in joints other than the knee have not been established.
- The safety and effectiveness of the use of GenVisc 850 concomitantly with other intra-articular injectable products have not been established.

STERILE CONTENTS

The prefilled syringe is intended for single use. The contents of the syringe must be used immediately once the container has been opened. Discard any unused GenVisc 850.

INFORMATION FOR PATIENTS

- Transient pain and/or swelling of the injected joint may occur after intra-articular injection of GenVisc 850.
- 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 the 48 hours that follow the intra-articular injection.

Use in Specific Populations

- **Pregnancy**: The safety and effectiveness of GenVisc 850 have not been established in pregnant women.
- **Nursing Mothers**: It is not known if GenVisc 850 is excreted in human milk. The safety and effectiveness of GenVisc 850 have not been established in lactating women.
- **Pediatrics**: The safety and effectiveness of GenVisc 850 have not been demonstrated in children (21 years of age or younger).

ADVERSE EVENTS

The primary evidence of safety is provided by the comparison of GenVisc 850 to Phosphate Buffered Saline (PBS) in the AMELIA (Navarro, Spain) study[2]. In this study, four cycles of 5 injections of GenVisc 850 or PBS were administered with an interval of 6 months for the first three cycles and 1 year for the fourth cycle. Patients were followed for 1 year after the last injection. The population of patients evaluated for the safety of GenVisc 850 included 306 subjects (153 GenVisc 850, 153 PBS). In each treatment group, 127 subjects experienced at least one adverse event during the study and 22 patients (11 in each treatment group) experienced at least one adverse event that was reported as possibly, probably or certainly related to the device, Table 1. None of the related adverse events were assessed as severe. For the first cycle of 5 injections in the GenVisc 850 treatment group, the 15 adverse events reported as related were pain at the injection site (6), allergic reaction (3), arthralgia (2), bleeding at the injection site (2), bleeding (1) and heaviness (1). In the first cycle of 5 injections for the PBS treatment group, the 14 adverse events reported as related were bleeding at the injection site (6), allergic reaction (3), pain at the injection site (2), arthralgia (2), and arthritis (1).

Table 1: Related Adverse Events by Severity[2]

Related Adverse Events	GenVisc 850			PBS		
	Mild	Moderate	Total	Mild	Moderate	Total
Allergic reaction	2	1	3	3	--	3
Pain injection site	2	4	6	2	--	2
Bleeding	--	1	1	--	--	--
Bleeding injection site	2	--	2	6	--	6
Arthralgia	--	2	2	1	1	2
Arthritis	--	--	--	--	1	1
Heaviness	1	--	1	--	--	--
Total	7	8	15	12	2	14

A total of 513 complete GenVisc 850 treatment cycles and a total of 487 complete PBS treatment cycles were administered in the study. Table 2 provides the number of related adverse events per complete treatment cycle. The rate of adverse events per treatment cycle for GenVisc 850 is 0.029, which is the same as the PBS rate. This low adverse event rate demonstrates the safety of GenVisc 850 following repeat treatments.

Table 2: Related Adverse Events by Treatment Cycles

Treatment	No. Complete Cycles	No. Related Adverse Events	Related AEs per Complete Cycles
GenVisc 850	513	15	0.029
PBS	487	14	0.029

Supporting evidence of safety is provided by the comparison of GenVisc 850 to Supartz®/Supartz FX™ (sodium hyaluronate, Seikagaku Corp.) in the Yong Ping study. The population of patients evaluated for the safety of GenVisc included 229 subjects (116 GenVisc 850, 113 Supartz/Supartz FX). In the Supartz/Supartz FX group, 26 (23.0%) subjects experienced adverse events (AEs) and 6 (5.3%) of them, 4 cases of local pain and 2 cases of swelling, were judged possibly related to the device. In the GenVisc 850 group, 21 (18.1%) subjects experienced AEs and 2 (1.7%) of them, 1 case of local pain and 1 case of rash, were judged possibly related to the device. There were no statistically significant differences in the incidence rates of these adverse events between the GenVisc 850 and Supartz/Supartz FX groups. A summary of AEs is provided in Table 3.

Table 3: Adverse Events Reported in Yong Ping Study

	Category	Supartz/Supartz FX Group/N (%)	GenVisc 850 Group/N (%)	Statistics	P value	Method
AE	Yes	26 (23.0)	21 (18.1)	0.844	0.358	Chi-square
	No	87 (77.0)	95 (81.9)			
	Total	113	116			
Related AE	Yes	6 (5.3)	2 (1.7)	--	0.167	Fisher
	No	107 (94.7)	114 (98.3)			
	Total	113	116			
SAE	Yes	1 (0.9)	0 (0.0)	--	1.000	Fisher
	No	112 (99.1)	116 (100.0)			
	Total	113	116			

Note: AEs that were definitely related, probably related, or possibly related to the device, and abnormal laboratory findings were judged as Related AEs.

GenVisc 850 has been commercially distributed in 40 countries outside of the United States. GenVisc is also approved in 23 other countries but not presently distributed. GenVisc 850 (sold ex-U.S. as Adant) has been on the market in Japan since 1995 and in Europe since 1996. From the time of its first marketing through 2012 over 35 million syringes were distributed with no major safety concerns related to the product.

CLINICAL STUDIES

The results of the Yong Ping study and the Bayesian longitudinal analysis summarized below confirm that the clinical performance of GenVisc 850 was superior to a saline placebo control and similar to that of Supartz/Supartz FX. The Yong Ping study was a randomized controlled, multicenter clinical trial that demonstrated non-inferiority of GenVisc 850 to Supartz/Supartz FX through 6 weeks. The Bayesian longitudinal analysis included data from four randomized controlled trials, two of which included comparisons of GenVisc 850 to saline and two of which included comparisons of Supartz/Supartz FX to saline. The results of this Bayesian longitudinal analysis demonstrated the superiority of GenVisc 850 to a saline placebo control.

Yong Ping (2012): Head-to-Head (GenVisc 850 vs. Supartz/Supartz FX) Randomized Controlled Study

The Yong Ping study was a parallel-controlled, randomized, multi-center clinical conducted at five hospitals. The objective of the trial was to evaluate the comparative efficacy and safety of GenVisc 850 intra-articular injections for the treatment of degenerative osteoarthritis knee pain to Supartz/Supartz FX.

A total of 229 subjects were enrolled with 113 in the Supartz/Supartz FX treatment group and 116 in the GenVisc 850 group. Of those, 92.9% and 93.1% in the Supartz/Supartz FX and GenVisc 850 groups, respectively, completed the trial. Each group received 5 injections of the respective product at weekly intervals.

The average age was 62.3 years in the Supartz/Supartz FX group and 74% of the subjects were female. The average age was 61.9 years in the GenVisc 850 group and 80% of the subjects were female. In both groups, the average weight was 66 kg. There were no statistically significant differences in demographic characteristics.

Primary Effectiveness: In the full analysis set (FAS) population, the VAS pain on movement of the Supartz/Supartz FX group at week 6 decreased by 48.0±23.39 mm compared to baseline, and that of the GenVisc 850 group decreased by 49.2±21.50 mm. The difference between the two groups was not statistically or clinically significant (P>0.05). These analyses are shown in Table 4.

Table 4: VAS pain on movement (mm) and baseline variations (Week 6 - Baseline) (FAS)

	Supartz/ Supartz FX group	GenVisc 850 group	Statistics	P value	Method
N	113	116	0.403	0.688	t test
Mean±SD	–48.0±23.39	–49.2±21.50			
95%CI(Lower-Upper)	–52.33-–43.61	–53.12-–45.21			
Min-Max	–95.0-1.00	–90.0-17.00			
Median	–50.00	–50.25			

Meta-Analysis of 4 Studies Using Bayesian Modeling

To further support the clinical similarities between GenVisc 850 and Supartz/Supartz FX, a prospective meta-analysis of the pivotal studies for both products was undertaken using Bayesian longitudinal modeling. The studies analyzed include:

- For GenVisc 850, two saline-controlled studies (AMELIA[2] and Blanco[3]); and
- For Supartz/Supartz FX, two saline-controlled studies conducted in Australia[4] and Sweden[5].

Primary Objectives of the Bayesian Analysis:

- Supartz/Supartz FX is superior to PBS. The null hypothesis is that PBS is superior to Supartz/Supartz FX. Rejection of the null hypothesis will in effect validate the statistical approach and modeling as it duplicates the results of the approved PMA for Supartz/Supartz FX.
- GenVisc 850 is superior to PBS. The non-inferiority margin for addressing this objective is 4 mm.

Supporting Objective of the Bayesian Analysis:

- GenVisc 850 advantage over PBS is non-inferior to Supartz/Supartz FX's advantage over PBS. The non-inferiority margin for addressing this objective is 4 mm.

Results of Meta-Analysis of 4 Studies Using Bayesian Modeling

Primary Analysis: For the primary analysis, which pools all data from post-baseline visits for all treatments in all studies, the estimated between-study variability (T) was examined and found to be acceptable for superiority and non-inferiority assessments.

The Gelman-Rubin convergence statistic was very close to 1, thus indicating convergence of the sampler. Overall the model fits the data well.

Primary Analysis

The posterior probability of superiority of GenVisc 850 vs. PBS is 79% at week 30 (mean 6.88 mm advantage) thus giving confidence that GenVisc 850 is superior to PBS up to 30 weeks.

Secondary Analysis

For the primary and supporting analyses, differences in mean change from baseline between GenVisc 850 and PBS were examined. Paucity of data towards the end of the time interval causes an increase in variance and therefore the posterior probability of non-inferiority does not increase. The posterior mean difference between effect GenVisc 850 and Supartz/Supartz FX was always below the non-inferiority margin with a posterior probability of 50%, but the scarcity of data limits the ability to declare non-inferiority of GenVisc 850 to Supartz/Supartz FX for the interval extending to 30 weeks.

Further details of the primary and secondary analysis assessments are provided below in Table 5 and Figure 1.

Table 5. Posterior Probabilities for Main Analysis of GenVisc 850 Superiority

Objective	π	Probability
GenVisc Superiority	π_1	79

The results of the longitudinal analyses are presented in support of the observation that GenVisc 850 is superior to PBS across time. There is a good linear fit of the data to the model demonstrating increasing mean differences between GenVisc 850 and PBS through 30 weeks, Figure 1.

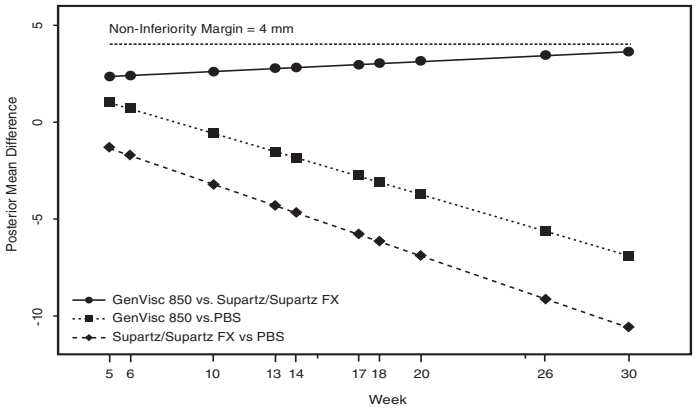

Figure 1. Treatment Difference Estimates Across Time Using a Linear Trend Longitudinal Model.

DETAILED DEVICE DESCRIPTION

Each 3mL prefilled syringe of GenVisc 850 contains:

Sodium Hyaluronate	25.0mg
Sodium Chloride	21.3mg
Disodium Phosphate Dodecahydrate	1.5mg
Sodium Hydroxide	q.s. to adjust pH
Hydrochloric acid	q.s. to adjust pH
Water for Injection	q.s. 2.5mL

HOW SUPPLIED

GenVisc 850 is supplied as a sterile, non-pyrogenic solution in 3mL pre-filled syringe.

DIRECTIONS FOR USE

GenVisc 850 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. Injection of subcutaneous lidocaine or similar local anesthetic may be recommended prior to injection of GenVisc 850.

Warning: Do not concomitantly use disinfectants containing quaternary ammonium salts for skin preparation because sodium hyaluronate can precipitate in their presence.

Precaution: Do not use GenVisc 850 if the package is opened or damaged. Store in the original packaging (protected from light) below 86°F (30°C). DO NOT FREEZE. Do not use after expiration date indicated on package. The shelf life is 36 months.

Precaution: Strict aseptic administration technique must be followed.

Precaution: Remove joint effusion, if present, before injection GenVisc 850.

Take care to remove the tip cap of the syringe and needle aseptically. Inject GenVisc 850 into the joint through a 21-23 gauge needle.

Inject the full 2.5mL in one knee only. If treatment is bilateral, a separate syringe should be used for each knee.

Precaution: The prefilled syringe is intended for single use. The content of the syringe must be used immediately once the container has been opened. Discard any unused GenVisc 850.

MANUFACTURED BY:
TEDEC MEIJI FARMA (SPAIN)
Ctra. M-300, Km 30,500
28802 Alcalá de Henares (Madrid) Spain

DISTRIBUTED BY:
OrthogenRx, Inc.
Pennsylvania Biotechnology Center
3805 Old Easton Road
Doylestown, Pennsylvania 18902-8400
1-844-GenVisc (1-844-436-8472)

[1] GenVisc® is a registered trademark of OrthogenRx, Inc. GenVisc 850 is sold outside the U.S. under the branded name Adant®, a registered trademark of Meiji Seika Pharma Co., Ltd.

[2] Navarro-Sarabia F, Coronel P, Collantes E, Navarro FJ, de la Serna AR, Naranjo A, Gimeno M, Herrero-Beaumont G; AMELIA study group. A 40-month multicentre, randomised placebo-controlled study to assess the efficacy and carry-over effect of repeated intra-articular injections of hyaluronic acid in knee osteoarthritis: the AMELIA project. Ann Rheum Dis. 2011;70: 1957-62.

[3] Blanco FJ, Fernández-Sueiro JL, Pinto-Tasende JA, Fernández-López JC, Ramallal M, Freire A et al. Intra-articular hyaluronan treatment of patients with knee osteoarthritis waiting for replacement surgery. The Open Arthritis Journal 2008; 1: 1-7.

[4] Day, R. et al. A double blind, randomized, multicenter, parallel group study of the effectiveness and tolerance of intraarticular hyaluronan on osteoarthritis of the knee. J Rheumatol 2004; 31: 755-782.

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