SUPARTZ FX™
sodium hyaluronate

(sodium hyaluronate)

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

DESCRIPTION
SUPARTZ FX is a sterile, viscoelastic non-pyrogenic solution of purified, high molecular weight (620,000-1,170,000 daltons) sodium hyaluronate (hyaluronan) having a pH of 6.8-7.8. Each one mL of SUPARTZ FX contains 10 mg of sodium hyaluronate (hyaluronan) dissolved in a physiological saline (1.0% solution). The sodium hyaluronate (hyaluronan) is extracted from chicken combs. Sodium hyaluronate (hyaluronan) is a polysaccharide containing repeating disaccharide units of glucuronic acid and N-acetylglucosamine.

INDICATIONS AND USAGE
SUPARTZ FX 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
General
- The effectiveness of a single treatment cycle of less than 3 injections has not been established.
- Strict aseptic administration technique must be followed.
- Remove joint effusion, if present, before injecting SUPARTZ FX.
- The safety and effectiveness of the use of SUPARTZ FX in joints other than the knee have not been established.
- The safety and effectiveness of the use of SUPARTZ FX concomitantly with other intra-articular injectables have not been established.
- Use caution when injecting SUPARTZ FX into patients who are allergic to avian proteins, feathers and egg products.
- 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 SUPARTZ FX.
- Do not use SUPARTZ FX if the package is opened or damaged. Store in the original packaging below 77°F (25°C). DO NOT FREEZE. Do not use after expiration date indicated on package. Shelf life is 42 months.

INFORMATION FOR PATIENTS
- Provide patients with a copy of the Patients' Information prior to use.
- Transient pain and/or swelling of the injected joint may occur after intra-articular injection of SUPARTZ FX.
- 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.
- The effectiveness of repeat treatment cycles of SUPARTZ FX has not been established.

Use in Specific Populations
- Pregnancy: The safety and effectiveness of SUPARTZ FX have not been established in pregnant women.
- Nursing Mothers: It is not known if SUPARTZ FX is excreted in human milk. Excretion has been seen in rat milk. The safety and effectiveness of SUPARTZ FX have not been established in lactating women.
- Pediatrics: The safety and effectiveness of SUPARTZ FX have not been demonstrated in children.

ADVERSE EVENTS
The evaluable for safety population included all patients receiving at least one injection (532 SUPARTZ FX 5; 87 SUPARTZ FX 3; 537 control injection) in five well controlled clinical trials. The most common adverse events occurring in SUPARTZ FX-treated patients were arthralgia, defined as joint pain with no evidence of inflammation, arthropathy/arthrosis/arthritis, defined as joint pain with evidence of inflammation, back pain, pain (non-specific), injection site reaction, headache, and injection site pain (See Table 1). There were no statistically significant differences in the incidence rates of these adverse events between treatment groups.

Five (5) allergic reactions were reported in the SUPARTZ FX group. All five events were classified as mild to moderate. These were: hayfever (2), reaction on face and neck, cutaneous reaction forearms and knees, and an undefined mild allergy reaction. No anaphylactic reactions were observed in any study patients. Other adverse events occuring in 4% or less but not less than 1% of the SUPARTZ FX treated patients included upper respiratory tract infection, influenza-like symptoms, nausea, sinusitis, urinary tract infection, bronchitis, abdominal pain, diarrhea, inflicted injury, leg pain, discomfort in legs, dyspepsia, dizziness, rhinitis, and fall.

SUPARTZ FX (ARTZ) has been in use in Japan since 1987. A prospective post-market surveillance study[1] conducted from 1987 to 1993 evaluated safety on 7404 knees treated from a total of 675 medical institutions. A subset of 7155 knees was treated with 3 or more consecutive injections. There were 58 cases of adverse reactions in 37 knees (0.50% - 37/7404). The most frequently observed were 29 cases of pain at the injection site, 16 cases of swelling, and 3 cases of redness. Other adverse reactions were 3 cases of rash, 3 cases of increased serum GPT, 2 cases of increased serum GOT, 1 case of itching, and 1 case of increased Al-P. The incidence of adverse reactions was not related to the number of injections. There was no increase in adverse events in patients requiring 3 or more injections.

Adverse experience data from the literature contain no evidence of increased safety risk relating to retreatment with SUPARTZ FX. The frequency and severity of adverse events occurring during repeat treatment cycles did not increase over that reported for a single treatment cycle.

Post-market experience: The following possible adverse reactions have been reported worldwide.
- The most common adverse reactions include: Injection site reactions (pain / swelling / effusion / redness / warmth). Rare cases of severe reactions have been reported.
- Other adverse reactions include: Itching; swelling of the face, eyelids, mouth and/or extremities; rash; hives; redness in face; nausea; vomiting and fever. Anaphylactic/anaphylactoid reactions accompanied by transient hypotension (sudden drop in blood pressure), have been rarely reported, all of which resolved either spontaneously or after conservative treatment.

CLINICAL STUDIES
Study Design
The safety and effectiveness of SUPARTZ FX was based on an integrated analysis of five randomized, multi-center, blinded, "placebo controlled" clinical trials. Entry criteria are described for all studies (See Table 2). The treatment regimen consisted of 5 weekly injections in all studies. All patients in these studies (including those injected with the control) received arthrocentesis of the knee prior to an injection of SUPARTZ FX or vehicle (phosphate buffered saline) or, in the German study only, a dilute (1%) form of the SUPARTZ FX formulation. The French study included an additional treatment arm: 3 SUPARTZ FX injections followed by 2 injections of the control per patient. (Table 3 describes the study design and the treatment and follow-up schedules.)

Measures of Effectiveness
Table 3 provides details of the primary and secondary effectiveness parameters used in each study. The Lequesne Index[2], although a primary measure of effectiveness in only three studies (France, Germany, and Sweden) was common to all five studies. It was used for the integrated analysis of effectiveness across all five studies. The primary measure used in the other two studies was the WOMAC Index in Australia[3], and VAS pain ratings in the United Kingdom.

Results
Patient Population and Demographics
The demographics of study participants were comparable across treatment groups with respect to age, sex, mean body mass index, and baseline scores, with the exception of gender in the German study (see Table 4).

Individual Study Results
Medication use results are presented in Table 5. The results for the Australian study for the protocol-specific primary analysis are presented in Table 6A. The results for all studies of analysis of the Lequesne score as repeated measures analysis of covariance (ANCOVA) of mean reduction from baseline over all visits at or following the 5 week visit are presented in table 6B. Other analyses are as follows: The results for the German study of the paracetamol consumption performed as a non-parametric ranking procedure (stratified Wilcoxon rank-sum test), over weeks 1-5, are SUPARTZ FX = 0.85 and Control = 0.89 ($p > 0.05$). The results for the Swedish and UK studies for the protocol-specific primary analysis = VAS ratings as analysis of covariance (ANCOVA) at weeks 1-5, 13 and 20 (Swedish study), and repeated measures analysis of variance (ANOVA), over weeks 10, 14, and 18, (UK study) are the following: SUPARTZ FX = 10.11 and Control = 9.76 for the Swedish study ($p > 0.05$); and SUPARTZ FX = 13.47 and Control = 12.89 for the UK study ($p > 0.05$).

Integrated Analysis
An integrated longitudinal analysis was conducted to examine results across all five studies. See Table 6C. This method of analyzing data with repeated measurements takes into account the correlation structure of the repeated measurements and examines the effects of treatment over time. The integrated longitudinal analysis showed a reduction in the total Lequesne score of 2.68 in the SUPARTZ FX treatment groups compared to a reduction in the total Lequesne score of 2.00 in the control groups ($p=0.0026$). The 95% confidence interval for the difference of the reduction in total Lequesne score between SUPARTZ FX and control is (0.56, 0.79).

Summary of Results
The difference in reduction in total Lequesne scores between the SUPARTZ FX treated group and the control group is 0.68, which is statistically significant in the integrated analysis ($p=0.0026$). Additionally, the Australian study shows a significant difference between SUPARTZ FX and control in both the WOMAC pain ($p=0.045$) and stiffness ($p=0.024$) scores and Lequesne total scores ($p=0.0114$).

DETAILED DEVICE DESCRIPTION
Each 2.5 mL prefilled syringe of SUPARTZ FX contains:

Sodium Hyaluronate (hyaluronan)	25.0 mg
Sodium Chloride	21.25 mg
Dibasic Sodium Phosphate Dodecahydrate	1.343 mg
Sodium Dihydrogen Phosphate Dihydrate	0.04 mg
Water for Injection	q.s.

HOW SUPPLIED
SUPARTZ FX is supplied as a sterile, non-pyrogenic solution in 2.5 mL pre-filled syringe.

DIRECTIONS FOR USE
SUPARTZ FX is administered by intra-articular injection once a week (1 week apart) for a total of 5 injections. Some patients may experience benefit with 3 injections given at weekly intervals. This has been noted in a study in which patients treated with three injections were followed for 90 days[4]. Injection of subcutaneous lidocaine or similar local anesthetic may be recommended prior to injection of SUPARTZ FX.

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 SUPARTZ FX if the package is opened or damaged. Store in the original packaging below 77°F (25°C). DO NOT FREEZE. Do not use after expiration date indicated on package. Shelf life is 42 months.

Precaution: Strict aseptic administration technique must be followed.

Precaution: Remove joint effusion, if present, before injection of SUPARTZ FX.

Take care to remove the tip cap of the syringe and needle aseptically. Inject SUPARTZ FX into the joint through a 22-23 gauge needle.

Inject the full 2.5 mL 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 SUPARTZ FX.

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Reference
[1]Ueno, Y. et al. Investigation on result of use after launch of ARTZ and ARTZ Dispo: Evaluation on the efficacy, safety and utility in the medication for osteoarthritis of the knee and periarthritis of the shoulder. Japanese Pharmacology & Therapeutics 23(8):2151-2170, 1995.

[2]Lequesne MG: The algofunctional indices for hip and knee osteoarthritis. J Rheumatol 24: 779-81, 1997.

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

[4]Karlsson, J. et al. Comparison of two hyaluronan drugs and placebo in patients with knee osteoarthritis. A controlled, randomized, double blind, parallel-design multicentre study. Rheumatology (Oxford). 2002 Nov; 41(11):1240-8.

Table 1: Adverse Events Occurring in > 4% of SUPARTZ FX-treated Patients

Integrated Safety Database	SUPARTZ FX (n=619)		Control (n=537)	
	n	%	n	%
Arthralgia	110	17.8%	95	17.7%
Arthropathy/Arthrosis/Arthritis	68	11.0%	57	10.6%
Back Pain	40	6.5%	26	4.8%
Pain (non-specific)	37	6.0%	26	4.8%
Injection Site Reaction*	35	5.7%	18	3.4%
Headache	27	4.4%	23	4.3%
Injection Site Pain	26	4.2%	22	4.1%

*Includes application/injection site reaction, injection site inflammation, and purpura injection site.

***Table 1A: Adverse Events Occurring in 3-Injection SUPARTZ FX-treated Patients**

Adverse Event Type	French Study	
	Number (%) of Patients Receiving Control Injections (N=80)	Number (%) of Patients Receiving SUPARTZ FX-3 (N=87)
Arthralgia	12(15.0%)	11(12.6%)
Arthropathy, Arthrosis or Arthritis	3(3.8%)	1(1.1%)
Back Pain	10(12.5%)	10(11.5%)
Pain	16(20.0%)	16(18.4%)
Injection Site Reaction*	0(0.0%)	1(1.1%)
Headache	4(5.0%)	3(3.4%)
Injection Site Pain	4(5.0%)	3(3.4%)

*Includes application/injection site reaction, injection site inflammation, and purpura injection site.

Table 2: Entry Criteria

	Inclusion				Exclusion
Study	**Baseline pain level**	**Duration of pain prior to study entry**	**Unilateral versus bilateral**	**Radiologic criteria**	**Effusion**
Australia	Not specified	≥ 3 months	Unilateral or predominantly unilateral**	Evidence of one or more of the following features in an x-ray taken during the previous 6 months: femorotibial osteophytes, osteosclerosis of the femoral or tibial endplates, or joint space narrowing	> 50 mL
France	Lequesne total score = 4 - 12 Global pain ≥ 35 mm on VAS	≥ 3 months	Unilateral or Predominantly unilateral**	Narrowing of femorotibial space > 20% and < 90% in at least 1 of the appropriate angles and/or OA and/or osteocondensation, and/or geode(s)	Severe (tight, distending effusion)
Germany	Moderate to medium*	Not specified	Unilateral or bilateral	Osteophytes	> 100 mL
Sweden	Not specified	Not specified	Unilateral	Knee flexion angle of 10 - 15°; 50 - 100% obliteration (= 400 mm) of the joint space (standing radiographs) without any bone erosion	Not specified
United Kingdom	Moderate*	> 3 months	Unilateral or predominantly unilateral**	Femorotibial osteophytes	> 50 mL

* Definition not specified in protocol.
** Predominantly unilateral means that even in the case of bilateral disease it is possible for the patient to identify one predominant knee that is affected, as reported by the investigator.

Table 3: Prospective, Randomized Clinical Studies of Symptomatic OA Patients - Study Design

Study	Control	Effectiveness Parameters	Evaluation Timepoints	Protocol-Specified Analysis Plan for Primary Effectiveness Analysis	Concurrent OA therapy
Australia	Arthrocentesis Injection with phosphate buffered saline	Primary - WOMAC pain, stiffness, and disability Secondary - Lequesne, Paracetamol Consumption, Investigator Global Assessment, Patient Global Assessment	Week 0, 1*, 2, 3, 4, 5, 6, 10, 14, 18	Repeated measures analysis of covariance (ANCOVA) of mean reduction from baseline for WOMAC pain, stiffness, and disability, over weeks6, 10, 14, and 18.	Paracetamol Rescue
France**	Arthrocentesis Injection with phosphate buffered saline	Primary - Lequesne Secondary - VAS Ratings, Paracetamol Consumption, Investigator Global Assessment	Screen, Day 0*, 7, 14, 21, 28, 35, 60, 90	Analysis of variance (ANOVA) of mean reduction from baseline for Lequesne scores, at days 35, 60, and 90.	Paracetamol Rescue
Germany	Arthrocentesis Injection with a dilute (1%) formulation of SUPARTZ FX	Primary - Lequesne, Paracetamol Consumption Secondary - VAS Ratings, Investigator Global Assessment, Patient Global Assessment	Week 0, 1*, 2, 3, 4, 5, 6, 10, 14	1. Repeated measures ANCOVA of mean reduction from baseline for Lequesne scores, over weeks 4, 5, and 6. 2. Non-parametric ranking procedure applied to mean reduction from baseline for paracetamol consumption, over weeks 1-5.	Paracetamol Rescue
Sweden	Arthrocentesis Injection with phosphate buffered saline	Primary - Lequesne, VAS Ratings for knee function, knee pain, range of motion, and activity level Secondary - Paracetamol Consumption, Investigator Global Assessment, Patient Global Assessment	Week -1 , 0*, 1, 2, 3, 4, 5, 13, 20	ANCOVA of mean reduction from baseline for both Lequesne scores and VAS pain ratings, at weeks 1-5, 13, and 20.	Paracetamol Rescue
United Kingdom	Arthrocentesis Injection with phosphate buffered saline	Primary - VAS Pain Ratings Secondary - Lequesne, Paracetamol Consumption, Investigator Global Assessment, Patient Global Assessment	Week 0, 1*, 2, 3, 4, 5, 6, 10, 14, 18, 26	Repeated measures ANOVA of mean VAS pain ratings, over weeks 10, 14, and 18.	Co-Proxamol Rescue

* First injection given
** This study had 3 treatment arms: 3 injections of SUPARTZ FX, 5 injections of SUPARTZ FX, control

Table 4: Patient* Demographics by Treatment Group

Country	# of Centers	# of Patients			Age (Mean)	% Female	BMI	Baseline Total Lequesne
		Total	SUPARTZ FX	Control				
Australia	17	223	108	115	A = 62.4 C = 63.0	A = 56.5 C = 61.7	A = 29.5 C = 29.2	A = 12.1 C = 13.0
France	54	254	(5) 87 (3) 87	80	A (5) = 64.7 A (3) = 63.9 C = 65.2	A (5) = 60.9 A (3) = 73.6 C = 68.8	A (5) = 27.4 A (3) = 28.3 C = 28.5	A (5) = 9.8 A (3) = 9.8 C = 10.1
Germany	25	208	102	106	A = 62.0 C = 60.5	A = 70.6** C = 56.6	A = 26.2 C = 26.8	A = 10.5 C = 9.6
Sweden	8	239	119	120	A = 58.5 C = 58.0	A = 55.5 C = 55.8	A = 27.7 C = 27.2	A = 9.9 C = 9.6
UK	19	231	116	115	A = 60.8 C = 61.6	A = 60.3 C = 53.9	A = 28.7 C = 28.2	A = 13.5 C = 13.5
Total	123	1155	619	536***				

* All ITT Patients
** Percent female was statistically significantly higher in the SUPARTZ FX group
*** One patient is excluded from this table since no efficacy data was collected/available
A = SUPARTZ FX (5) = 5 Injections, France
C = Control (3) = 3 Injections, France

Table 5: % Distribution of Patients* Using Analgesic and Anti-inflammatory Drugs by Treatment Group

Medication	Country									
	Australia Total #s of Patients SUPARTZ FX = 108 Control = 115		France Total #s of Patients SUPARTZ FX = (5)87/(3)87 Control = 80		Germany Total #s of Patients SUPARTZ FX = 102 Control = 106		Sweden Total #s of Patients SUPARTZ FX = 119 Control = 120		UK Total #s of Patients SUPARTZ FX = 116 Control = 115	
	n	%	n	%	n	%	n	%	n	%
Aspirin										
SUPARTZ FX	5	4.6%	2	2.3%	1	1.0%	29	24.4%	9	7.8%
SUPARTZ FX (3)**			3	3.4%						
Control	10	8.7%	0	0.0%	1	0.9%	37	30.8%	15	3.0%
Paracetamol***										
SUPARTZ FX	85	78.7%	74	85.1%	73	71.6%	59	49.6%	108	93.1%
SUPARTZ FX (3)**			74	85.1%						
Control	97	84.3%	71	88.8%	81	76.4%	56	46.7%	106	92.2%
Codeine Compounds										
SUPARTZ FX	25	23.1%	18	20.7%	0	0%	19	16.0%	56	48.3%
SUPARTZ FX (3)**			18	20.7%						
Control	30	26.1%	21	26.3%	0	0%	24	20.0%	46	40.0%
Dextropropoxyphene										
SUPARTZ FX	0	0.0%	0	0%	0	0%	11	9.2%	0	0%
SUPARTZ FX (3)**			0	0%						
Control	2	1.7%	0	0%	0	0%	20	16.7%	0	0%
NSAIDs										
SUPARTZ FX	42	38.9%	47	54.0%	1	1.0%	59	49.6%	41	35.3%
SUPARTZ FX (3)**			41	47.1%						
Control	49	42.6%	49	61.3%	1	0.9%	48	20.0%	48	41.7%
Methylprednisolone										
SUPARTZ FX	2	1.9%	0	0%	0	0%	0	0%	0	0%
SUPARTZ FX (3)**			0	0%						
Control	5	4.3%	0	0%	0	0%	0	0%	0	0%

* All ITT Patients, patients with multiple types of medication use are counted for each type of medication
** All studies had 5 SUPARTZ FX injections. In the French study, there was an additional treatment arm with 3 SUPARTZ FX injections.
*** Includes paracetamol consumption as provided per protocol as rescue medication, as well as any additional paracetamol use.

Table 6A: Australia Study Results for WOMAC (Pain, Stiffness, & Disability) as Repeated Measures Analysis of Covariance (ANCOVA) of Mean Reduction from Baseline Over Weeks 6, 10, 14, and 18

Treatment	Pain	Stiffness	Disability
SUPARTZ FX	2.72*	1.37*	9.21
Control	2.23	0.99	7.51

* = p-value < 0.05

Table 6B: Individual Study Results for Lequesne Score as Repeated Measures Analysis of Covariance (ANCOVA) of Mean Reduction from Baseline Over All Visits at or Following the 5 Week Visit

Study	SUPARTZ FX (5 Injections)	SUPARTZ FX (3 Injections)	Control
Australia	2.85*		1.98
France	3.08	3.14	2.64
Germany	3.87		2.74
Sweden	1.68		1.77
UK	2.19*		1.53

* = p-value < 0.05

Table 6C: Integrated Analysis (All Five Studies) for Lequesne Score as Repeated Measures Analysis of Covariance (ANCOVA) of Mean Reduction from Baseline Over All Visits at or Following the 5 Week Visit

Study	SUPARTZ FX	Control
All Studies	2.68*	2.00

* = p-value < 0.05

Table 6D: Mean Changes from Baseline at 5, 9 and 13 weeks for VAS Pain and Lequesne Scores in the French Study ITT Population

Outcome Measure	Treatment Group	N	Evaluation			
			Baseline	Week 5*	Week 9*	Week 13*
Lequesne Index	Control	80	10.1	-2.6	-3.0	-3.1
	SUARTZ FX (3)	87	9.8	-2.6	-3.3	-3.5
	SUARTZ FX (5)	87	9.8	-2.7	-3.1	-3.3
VAS Pain	Control	80	59.8	-23.1	-26.5	-24.2
	SUARTZ FX (3)	87	57.9	-22.3	-26.0	-29.1
	SUARTZ FX (5)	87	56.9	-23.0	-26.2	-27.5

* All changes from baseline for all 3 treatment groups were statistically significant ($p < 0.0001$, Paired t-test).
SUPARTZ FX(3) = 3 SUPARTZ FX injections + 2 Control
SUPARTZ FX(5) = 5 SUPARTZ FX injections
Negative change indicates an improvement from baseline.

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