med supply
SOLUTIONS

SUPARTZ® (Italian) Product Specifications

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SUPARTZ™

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

INDICATIONS AND USAGE

SUPARTZ 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 5 injections has not been established.
- Strict aseptic administration technique must be followed.
- Remove joint effusion, if present, before injecting SUPARTZ.
- The safety and effectiveness of the use of SUPARTZ in joints other than the knee have not been established.
- The safety and effectiveness of the use of SUPARTZ concomitantly with other intra-articular injectables have not been established.
- Use caution when injecting SUPARTZ 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.
- Do not use SUPARTZ 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.
- 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 safety and effectiveness of repeat treatment cycles of SUPARTZ have not been established.

Use in Specific Populations

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

ADVERSE EVENTS

The evaluable for safety population included all patients receiving at least one injection (619 SUPARTZ; 537 control injection) in five well controlled clinical trials. The most common adverse events (occurring in greater than 4% of SUPARTZ-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 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 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.

CLINICAL STUDIES

Study Design

The safety and effectiveness of SUPARTZ 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 or vehicle (phosphate buffered saline) or, in the German study only, a dilute (1%) form of the SUPARTZ formulation. The French study included an additional treatment arm: 3 SUPARTZ injections followed by 2 injections of the control per patient. (Table 3 describes the study design and the treatment and followup schedules.)

Measures of Effectiveness

Table 3 provides details of the primary and secondary effectiveness parameters used in each study. The Lequesne Index, 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, 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

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 = 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 = 10.11 and Control = 9.76 for the Swedish study ($p > 0.05$); and SUPARTZ = 13.47 and Control = 12.89 for the UK study ($p > 0.05$). Medication use results are presented in Table 5.

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 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 and control is (0.56, 0.79).

Summary of Results

The difference in reduction in total Lequesne scores between the SUPARTZ 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 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 2.5mL prefilled syringe of SUPARTZ contains:

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

HOW SUPPLIED

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

DIRECTIONS FOR USE

SUPARTZ is administered by intra-articular injection once a week (1 week apart) for a total of 5 injections. Injection of subcutaneous lidocaine or similar local anesthetic may be recommended prior to injection of SUPARTZ.

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 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.

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

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Reference

'Lequesne MG: The algofunctional indices for hip and knee osteoarthritis. J Rheumatol 1997;24:779-81.

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

Integrated Safety Database	SUPARTZ (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 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 weeks 6, 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	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, 5 injections of SUPARTZ, control

Table 4: Patient* Demographics by Treatment Group

Country	# of Centers	# of Patients			Age (Mean)	% Female	BMI	Baseline Total Lequesne
		Total	SUPARTZ	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 group
***One patient is excluded from this table since no efficacy data was collected/available
A = SUPARTZ (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 = 108 Control = 115		France Total #s of Patients SUPARTZ = (5)87/(3)87 Control = 80		Germany Total #s of Patients SUPARTZ = 102 Control = 106		Sweden Total #s of Patients SUPARTZ = 119 Control = 120		UK Total #s of Patients SUPARTZ = 116 Control = 115	
	n	%	n	%	n	%	n	%	n	%
Aspirin										
SUPARTZ	5	4.6%	2	2.3%	1	1.0%	29	24.4%	9	7.8%
SUPARTZ (3)**			3	3.4%						
Control	10	8.7%	0	0.0%	1	0.9%	37	30.8%	15	3.0%
Paracetamol* **										
SUPARTZ	85	78.7%	74	85.1%	73	71.6%	59	49.6%	108	93.1%
SUPARTZ (3)**			74	85.1%						
Control	97	84.3%	71	88.8%	81	76.4%	56	46.7%	106	92.2%
Codeine Compounds										
SUPARTZ	25	23.1%	18	20.7%	0	0%	19	16.0%	56	48.3%
SUPARTZ (3)**			18	20.7%						
Control	30	26.1%	21	26.3%	0	0%	24	20.0%	46	40.0%
Dextropropoxyphene										
SUPARTZ	0	0.0%	0	0%	0	0%	11	9.2%	0	0%
SUPARTZ (3)**			0	0%						
Control	2	1.7%	0	0%	0	0%	20	16.7%	0	0%
NSAIDs										
SUPARTZ	42	38.9%	47	54.0%	1	1.0%	59	49.6%	41	35.3%
SUPARTZ (3)**			41	47.1%						
Control	49	42.6%	49	61.3%	1	0.9%	48	20.0%	48	41.7%
Methylprednisolone										
SUPARTZ	2	1.9%	0	0%	0	0%	0	0%	0	0%
SUPARTZ (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 injections. In the French study, there was an additional treatment arm with 3 SUPARTZ 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	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 (5 Injections)	SUPARTZ (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	Control
All Studies	2.68*	2.00

* = p-value < 0.05