

**SUMMARY OF SAFETY AND
EFFECTIVENESS DATA (SSED)**

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I. GENERAL INFORMATION

Device Generic Name:	Injectable Implant for Soft Tissue Augmentation
Device Trade Name:	Coaptite®
Applicant's Name and Address:	BioForm Medical, Inc. 1875 South Grant Street Suite 110 San Mateo, CA 94402
Date(s) of Panel Recommendations:	None
Pre-Market Approval Application (PMA) Number:	P040047
Date of Notice of Approval to the Applicant:	November 10, 2005

II. INDICATIONS FOR USE

COAPTITE® is indicated for soft tissue augmentation in the treatment of stress urinary incontinence (SUI) due to intrinsic sphincteric deficiency (ISD) in adult females.

III. CONTRAINDICATIONS

- In patients with significant history of urinary tract infections without resolution.
- In patients with current or acute conditions of cystitis or urethritis.
- In patients with fragile urethral mucosal lining.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Coaptite® labeling.

V. DEVICE DESCRIPTION

Coaptite® is an injectable, sterile, non-pyrogenic implant composed of spherical particles of calcium hydroxylapatite (CaHA) (75 - 125 microns in diameter), suspended in an aqueous based gel carrier. The gel carrier is composed of sodium carboxymethylcellulose, sterile water for injection, and glycerin. The gel carrier suspends the CaHA particles, allowing their delivery through injection needles, and is dissipated *in vivo*, while the CaHA particles remain at the injection sites to provide soft tissue augmentation.

Coaptite® is injected into the submucosal tissue of the urethra near the bladder neck. The mechanism of action is to augment the surrounding soft tissue causing a coaptation of the urethra, increasing urethral resistance to the loss of urine. The CaHA particles act as space-filling bulk for the urethral tissue.

VI. ALTERNATE PRACTICES AND PROCEDURES

Conventional procedures used in the treatment of female stress urinary incontinence include:

- behavioral techniques, such as bladder training and prompted voiding;
- pelvic floor strengthening exercises (i.e., Kegel exercises), with or without device assistance, such as biofeedback, vaginal cones, and electrical stimulation of the pelvic floor muscles;
- external devices, such as absorbent products (pads/diapers), collecting devices, or occluding devices;
- internal urethral occlusion devices;
- pharmacological treatments, such as alpha-adrenergic agonists and estrogen supplements;
- other injectable bulking agents such as Contigen®, Durasphere and Uryx®
- surgical treatments/procedures; such as suspension or sling procedures, and urinary diversion procedures.

VII. MARKETING HISTORY

Coaptite® was approved (received CE mark) for the treatment of SUI in Europe in January 2001.

Coaptite® has not been withdrawn from any market for any reason.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

The safety of Coaptite® for the treatment SUI is based upon a prospective, multicenter, single-blind study in which 158 Coaptite® patients with SUI due to ISD were treated and evaluated through a 12-month period after initial treatment and compared to a control.

The Coaptite® clinical study involved 307 Coaptite® treatments in 158 subjects with a mean follow-up of approximately 11.2 months. A total of 1265 adverse events were reported during the clinical study in 146 Coaptite® (696 events) and 131 control patients (569 events). There were two treatment related serious adverse events in two patients in the Coaptite® group. A detailed discussion of the adverse events is presented in the Safety section. In this section, only the serious adverse events and the genitourinary non-serious adverse events are discussed.

There were 33 serious adverse events in the study; 17 occurred in 11 Coaptite® patients and 16 occurred in 12 control patients. None of the 16 SAEs in the control group were considered treatment related. Of the 17 SAEs in Coaptite®

patients, two unanticipated SAEs (1.3%) were considered treatment related events involving dissection of Coaptite® through the tissue.

- In one patient, erosion of approximately 1 cm on the vaginal wall just proximal to the meatus was observed. Skin bridges extended between the erosion and the meatus. The meatus was disconnected from the underlying fascia of the urethra such that the erosion extended from the bladder neck to the meatus. In effect, vaginal wall overlying the urethra was no longer connected to the underlying structures and required corrective surgery.
- The 2nd patient with a history of pelvic surgery had failed her first bulking procedure with Coaptite® and underwent a 2nd bulking procedure. Six months after the 2nd procedure, cystoscopy revealed Coaptite® dissection into the bladder radially causing tissue bridges. The right ureteral orifice was not visualized and follow-up ultrasound showed pelviectasis and caliectasis. No corrective surgery was required.

There were no similar SAEs in the control group. There was one reported death of a patient with lung cancer who was injected with Coaptite® but it was determined not to be treatment related.

Table 1 presents details of the genitourinary NSAEs since these are the most relevant adverse events for urological procedures.

Table 1. Treatment Related Genito-urinary Non-Serious Adverse Events

Adverse Event	Coaptite® N=158			Control N=138		
	No. Patients	% Patients	No. Events	Number Patients	% Patients	Number Events
Urinary Retention	65	41.1%	99	46	33.3%	61
Hematuria	31	19.6%	48	17	9.4%	25
Dysuria	24	15.2%	32	13	9.4%	14
UTI	13	8.3%	18	14	10.1%	24
Urinary Urgency	12	7.6%	14	7	5.1%	7
Urinary Frequency	11	7.0%	12	8	5.8%	8
Urge Incontinence	9	5.7%	9	17	12.3%	20
Injection Site Pain	3	1.9%	4	2	1.5%	2
Genitourinary Infection	2	1.3%	2	2	1.5%	3
Erosion	2	1.3%	2	2	1.5%	2
Urine Analysis Abnormal	2	1.3%	3	0	0.0%	0
Pelvic Pain	1	0.6%	1	0	0.0%	0

Adverse Events reported for the Coaptite® group were similar to those reported for the Control group. Although not reported in the clinical study, other potential adverse events that may occur include erythema, embolic phenomena, and vascular occlusion.

IX. SUMMARY OF PRECLINICAL STUDIES

Material Characterization and Performance Testing

Testing of Coaptite® verified that the product met the required specifications in regard to the following:

- CaHA particle size (75-125 µ)
- pH (7.4 ± 0.6)
- X-ray Diffraction (typical of standard hydroxyapatite)
- Extrusion Force (≤ 15 lb force with a 7 Fr x 35 cm and 21 gauge needle)
- Sterility Assurance Level of 10⁻⁶
- Pyrogen Level of ≤ 20 EU/device

Validation testing was completed on the components (calcium hydroxylapatite, sterile water for irrigation, and sodium carboxymethylcellulose) as well as on the final packaged and sterilized Coaptite®.

The following bench tests were conducted to evaluate the performance characteristics of the final, packaged and sterilized Coaptite®.

- Injection Testing - Coaptite® can be extruded in one minute with an average force of approximately 9.8 pounds force (43.6 Newtons).
- Syringe Leakage - Safety testing demonstrated that the syringe, injection needle or the syringe Luer cap would not rupture with the maximum hand pressure of 30 pounds force (133 Newtons) applied to the syringe push rod using the finger grips.
- Simulated Use Testing - Coaptite®, as prepared for injection in primed injection needles, remained functional after twelve hours at room temperature conditions showing that its injectability is not affected by potential water loss.
- Particle Durability - The particles of calcium hydroxylapatite remained unchanged (no significant change in particle size distribution) after 3-4 years of implantation in dogs, demonstrating that the particles are durable.

Sterilization and Shelf-life Testing

Steam sterilization of Coaptite®-filled 1 cc syringes was validated to provide a sterility assurance level (SAL) of 10⁻⁶. Testing performed on the finished product verified that endotoxin levels were consistently maintained. The heat-sealing of the foil pouches has been validated and demonstrated to produce consistent seals with peel strengths of 5 pounds force. Real time and accelerated testing (at 45° C) on Coaptite® confirmed sterility and product functionality for a shelf-life of 36 months. These studies included simulation of shipping and handling conditions.

Biocompatibility Testing

In vitro and *in vivo* tests were based on ISO10993 (Biological Evaluation of Medical Devices)¹, using accepted test methods of biomedical materials or United States Pharmacopoeia references. These studies were conducted under

Good Laboratory Practice (GLP) guidelines. *In vitro* tests were performed to investigate cytotoxicity, blood interactions, and mutagenic responses. The test results indicated Coaptite® is nontoxic, non-sensitizing and non-mutagenic. Although Coaptite® was found to be hemolytic during testing, the hemolysis was attributed to the glycerin (a known hemolytic agent) found in the aqueous gel vehicle. The 36-month dog study and the clinical study discussed below have not reported any findings of clinical significance from this potential hemolytic reaction. Table 2 lists the various biocompatibility tests conducted and the results.

Table 2. Biocompatibility Test Results

Test	Results
Acute Systemic Toxicity (mice)	Non-Toxic
Intracutaneous Toxicity (rabbit)	Non-Toxic
Systemic Antigenicity (guinea pig)	Non-Antigenic
7-Day Muscle Implantation (rabbit)	Non-Irritant
28-Day Muscle Implantation (rabbit)	Non-Irritant
Cytotoxicity (Agar Overlay)	Non-Toxic
Ames Mutagenicity	Non-Mutagenic
Hemocompatibility (Clotting Time Lee-White)	No Significant Effect
Hemolysis	Hemolytic

Animal Studies: 36-month Dog Study

A 36-month implant study was conducted with Coaptite® in dogs. The objective of the study was to determine the tissue compatibility and migration potential of Coaptite®.

Using cystoscopic guidance, Coaptite® was injected into the periurethral tissue of the bladder neck in twenty-four (24) female dogs. Twelve (12) additional dogs were similarly injected with the gel carrier (Coaptite® without the calcium hydroxylapatite particles). Dogs assigned to the 12, 24 and 36-month groups were re-injected six months after the initial injection. Blood and urine samples were collected from each animal for routine hematology, clinical chemistry and urinalysis prior to study initiation, at six month intervals, and prior to termination.

Designated dogs were terminated at 1, 3, 6, 12, 25 and 36 months after initial injection. Each was necropsied; injection sites and other tissue inspected grossly; and implant sites and selected tissues processed for microscopic examination. All of the dogs tolerated the procedure well and remained in good health during the course of the study except one that was euthanized for a reason unrelated to the Coaptite® implantation.

The dog study reported the following significant findings:

- The hematology, clinical chemistry, urinalysis were acceptable throughout the study. All findings noted during necropsy were found to be within normal limits. There was no clinical evidence that the injection procedure or the Coaptite® caused untoward effects in the dogs.

- Microscopic evaluations of the implant sites at 1, 3, 6 and 12 months revealed two mixed but separate responses. A simple macrophage clearing response was associated with the sodium carboxymethylcellulose in the gel carrier of the Coaptite®. Most of the gel carrier disappeared at the 6-month time point. A delicate fibrous encapsulation was associated with the CaHA particles at all time points (3, 6, 12, 24 and 36 months). The Coaptite® at all time points was found as a well-defined injection site. The CaHA particles and the carrier remained at the injection site with no evidence of free migration. Some CaHA particles were found in distant tissues but this was considered an injection accident, not the result of migration. The accidental deposits of CaHA particles found in non-injection tissues resulted in no clinical response.
- While a small amount of CaHA had undergone degradation into small particles (< 10 μ size) at the 24- and 36-month time points and were engulfed and solubilized at the site by macrophages, most remained intact. Published literature on hydroxyapatite indicates that the breakdown into smaller particles occurs at the grain (fusion) boundaries of hydroxyapatite. The degradation into smaller particles and phagocytosis was similar to the degradation of hydroxyapatite implants used in the correction of bone defects. The CaHA particles engulfed by macrophages are cleared by reticuloendothelial system like any other foreign material of small size. Because of the degradation of CaHA particles into smaller size particles after 12 months of implantation, the macrophage response is expected to continue beyond the 36-month period until all CaHA is degraded into small particles and solubilized.

It was concluded from the biocompatibility testing and the dog study that Coaptite® is safe for injection into urinary bladder sites (urethral submucosa).

X. SUMMARY OF CLINICAL STUDIES

Study Design

The study was a prospective, randomized, comparative, single blind, parallel-group, multi-center clinical trial of Coaptite® and Control in female patients for soft tissue augmentation of the urethral sphincter with stress urinary incontinence (SUI) due to intrinsic sphincter deficiency (ISD), i.e., leak point pressure ≤ 100 cm H₂O and without associated urethral hypermobility as defined by resting or straining angle of ≤ 35° from horizontal of the bladder neck. Fourteen sites in the U.S.A. enrolled and treated the patients.

Five hundred forty five (545) patients were randomized after signing the informed consent. Patients were then screened to determine if they met the eligibility criteria (inclusion/exclusion) and passed the skin sensitization test. Two-hundred forty-nine (249) patients did not receive injections as they failed one or more of the screening tests, withdrew consent or for other reasons. Because randomization of the patients occurred before patient eligibility for treatment was determined, a true 1:1 distribution was not achieved, with slightly more patients receiving Coaptite® (158) than those receiving the Control (138). Protocol deviations occurred in 45 patients and were distributed equally between the two groups (23 Coaptite® and 22 Control).

All injections were performed by the investigators. Evaluations (baseline and post-procedure) that affected the efficacy variables and safety profile as defined in the protocol were performed by or under the direction of the investigator at each site.

Objective

The objective was to evaluate the safety and effectiveness of Coaptite® compared with the Control. The effectiveness evaluation was based on improvement on the Stamey Urinary Incontinence Scale (Stamey Grade). The safety evaluation was based on adverse events, physical examination, and laboratory test results.

Primary Effectiveness Endpoint

The primary effectiveness of Coaptite® as compared to the Control was measured by at least a one-grade improvement at 12 months after initial injection treatment over the baseline measurement of the Stamey Urinary Incontinence Scale.

The method used to evaluate the level of continence in the study was first defined by Stamey² in 1979 and is considered one of the standard scales to be used for these types of evaluations. The Stamey Scale has been used in previous clinical studies for other approved tissue bulking materials for the treatment of urinary incontinence. The grades within the Stamey Scale are defined as:

Grade 0: Continent (dry)

Grade 1: Urine leakage is associated with vigorous activities such as lifting weights, coughing or sneezing, but never in bed at night.

Grade 2: Urine leakage is associated with activities of minimal stress, such as walking or standing up.

Grade 3: Urine leakage occurs at all times regardless of activity or position.

Secondary Effectiveness Endpoints

In addition to Stamey Grade the following additional effectiveness endpoints were collected:

- Cure rate at 12 months using Stamey Grade, defined as the number of patients that were dry at 12 months (Grade 0).
- Significant improvement at 12 months using Stamey Grade, defined as a decrease in 2 or more grades at 12 months from baseline.
- Improvement in pad weight at 12 months using a 24-hour pad weight test, defined as a decrease of at least 50% in pad weight from baseline.
- Improvement in quality of life at 12 months using incontinence quality of life questionnaire (I-QOL), defined as mean improvement at 12 months from baseline.

Safety Endpoints

The safety assessment was defined as an acceptable safety and tolerability profile. This included evaluation of the incidence of treatment-related adverse

events by severity and causality, and detailed presentation of genitourinary adverse events.

Patient Selection

Inclusion criteria were:

- Female patients with urinary stress incontinence due to intrinsic sphincteric deficiency (leak point pressure ≤ 100 cm H₂O) and without associated urethral hypermobility (as defined by resting or straining angle of $\leq 35^\circ$ from horizontal of the bladder neck).
- Patients at least 18 years of age.
- Patient's continence had not shown any improvement in the last six months.
- Patient had failed prior noninvasive treatments (e.g., behavior modification, bladder exercises, biofeedback, electrical stimulation and/or drug therapy).
- Patient had good bladder function and a healthy bladder (bladder capacity greater than 250 ml and absence of detrusor instability).
- Patient had viable mucosal lining at likely site of injection (bladder neck).
- Patient had a negative urine culture as defined by midstream sample with an organism count of less than 10,000 and with no history of infection within a month of injection.
- Patient was mentally competent and able to understand all study requirements.
- Patient had a life expectancy of at least two years.
- Patient agreed to be available for the follow-up evaluations as required by the protocol.
- Patients who were willing to provide witnessed informed consent and who were willing and able to participate in all procedures and follow-up evaluation necessary to complete the study.

The exclusion criteria were:

- Patient had vesicoureteral reflux, spastic bladder, detrusor instability, or high pressure instability.
- Patient was on current medication for urinary incontinence.
- Patient had urinary incontinence for neurogenic etiology.
- Patient had current or acute conditions involving cystitis or urethritis.
- Patient used indwelling catheters for a long period of time and had fibrosis of the tissue at the likely injection sites.
- Patient had received pelvic radiotherapy and had fibrosis of the tissue at the likely injection sites.
- Patient was pregnant, lactating, or planning to become pregnant in the next twelve months.
- Patient had any condition which could lead to significant post operative complications, including current infection, uncontrolled diabetes, or elevated residual urine from bladder outlet obstruction.
- Patient had previous treatment of urinary incontinence with a urethral bulking agent.
- Patient had urinary incontinence primarily due to detrusor dysfunction (defined as detrusor insufficiency or detrusor hyperreflexia with detrusor contraction greater than 20 cm of water) associated with neurogenic illness or detrusor insufficiency with overflow incontinence.

- Patient had bladder capacity of less than 250 ml or post void residual volume of more than 50 ml.
- Patient was taking medication(s) primarily prescribed to affect urinary physiology (i.e., anticholinergic, adrenergic). Patient could be enrolled if drug(s) was discontinued and a wash out period of four weeks was observed prior to baseline testing.
- Patient was morbidly obese (defined as 100 pounds over their ideal body weight according to Metropolitan Life Insurance Company tables) and would not be expected to benefit from treatment.
- Patient with very short urethra and multiple urethral surgeries for stress incontinence who was not a candidate for injection treatment based upon the investigator's discretion.
- Patient had any condition that would preclude anesthesia or treatment due to contraindications and/or warnings in the experimental or control product labeling.
- Patient was actively immunosuppressed or allergic to bovine collagen product and/or lidocaine or had a positive reaction in the Control article skin test or was undergoing or intended to undergo desensitization injections to meat products.

Statistical Considerations

Coaptite® was considered non-inferior to the control if a 95% confidence interval (CI) for the difference in the primary efficacy variable was contained within the bounds of 15% of the control group proportion. The patients in the control group were expected to have primary efficacy variable success rate of 70%.

One hundred sixteen (116) patients per treatment group were required to achieve 15% bound of the two-sided 95% CI for the difference with an alpha = 0.05 and power = 80% (P1 = P2 =70%), provided that the primary efficacy variable in the control group is 70%. This means that 232 patients were required to have 12-month follow-up. Assuming a 20% drop out rate and 1:1 randomization to the two treatment groups, 280 patients needed to be treated and followed for 12 months.

Treatment

Patients that did not demonstrate a response to the skin test and who were otherwise eligible for treatment were treated. A treatment was defined as one or more injections of Coaptite® or the Control. That is, injections at one or more tissue sites in the urethra in one treatment session.

Soft tissue augmentation of the urethral sphincter was performed under anesthesia and with cystoscopic guidance. The anesthesia type and the route of injection were at the discretion of the investigator. The maximum total volume of Coaptite® that could be injected during one treatment session was fifteen (15) ml. The maximum number of treatments was limited to five (5) per patient.

If a satisfactory improvement was not achieved after the initial treatment, additional injection procedures were allowed during the first six months after the initial injection if the investigator determined that it was necessary. The additional injection procedures were to be scheduled a minimum of seven days from the previous procedure.

Follow-up Examination Schedule

All patients (Coaptite® and Control) were scheduled for follow-up examinations at 1, 3, 6, 9 and 12 months after the initial injection, with 48 Coaptite® patients followed for 24 months. Data collected at those examinations included physical examination, hypermobility assessment, uroflowmetry, urinalysis, cystometry, post cystometry pad test, 24-hour pad test, cystoscopic examination, quality of life, pelvic x-ray, voiding dairies laboratory tests, and Stamey scale rating.

Data Collection

During the baseline and follow-up visits, patient and medical history data relevant to the diagnosis of SUI, and data from laboratory testing, pad weight testing, voiding dairies and a quality of life (IQOL) assessment were collected. In addition to the assessment in changes in continence grades, data were also recorded on treatment related symptoms and adverse events.

Demographic Data and Baseline Data

Patients that received Coaptite® were adult females with an average age of 61 years. Table 3 presents the demographics and Table 4 presents baseline characteristics of the study population. There was no difference in the two patient groups for any of the patient demographics and/or baseline characteristics.

Table 3. Patient Demographics and Baseline Characteristics

Characteristic		Coaptite®	Control	p-Value
Age (yrs)	N	158	138	0.6998
	Mean	61.1	60.5	
	Std. Dev.	11.4	11.8	
	Median	60.0	60.0	
	Min.	37.0	32.0	
	Max.	87.0	87.0	
Urethral Length (cm)	N	158	138	0.8084
	Mean	3.0	3.0	
	Std. Dev.	0.7	0.7	
	Median	3.0	3.0	
	Min.	1.3	1.0	
	Max.	5.0	5.0	
Incontinence Type	N	158	138	0.7618
	Stress	131	112	
	Mixed	27	26	
Duration of Incontinence (Months)	N	158	138	0.3290
	Mean	122.5	110.0	
	Std. Dev.	106.1	113.0	
	Median	93.0	72.0	
	Min.	6.0	7.0	
	Max.	588.0	686.0	
Previous Treatments	N	158	138	
	Surgery	61 (38.6%)	48 (34.8%)	0.5464
	Medication	51 (32.3%)	46 (33.3%)	0.9014

Characteristic		Coaptite®	Control	p-Value
Post Void Residual (ml)	N	154	133	0.4639
	Mean	20.0	22.3	
	Std. Dev.	24.6	26.2	
	Median	15.0	18.0	
	Min.	0.0	0.0	
	Max.	175.0	200.0	
Leak Point Pressure (cm H ₂ O)	N	158	137	0.6856
	Mean	64.2	65.3	
	Std. Dev.	22.7	24.3	
	Median	65.0	68.0	
	Min.	10.0	11.0	
	Max.	134.0	162.0	
Race	N	158	138	0.8095
	Caucasian	140 (88.6%)	124 (89.9%)	
	African-American	3 (1.9%)	2 (1.5%)	
	Hispanic	12 (7.6%)	10 (7.3%)	
	Asian	1 (0.7%)	2 (1.5%)	
	Other	2 (1.3%)	0 (0.0%)	

Table 4. Patient Baseline Profile

Baseline Measure	COAPTITE® N = 158	Control N = 138
Mean Age in Years (Range)	61.1 (37.0 – 87.0)	60.5 (32.0 – 87.0)
Mean Duration of Incontinence in years (Range)	10.2 (0.5 – 49.0)	9.2 (0.6 – 57.2)
Mean Baseline Stamey Grade (Range)	2.3 (1 - 3)	2.5 (1 - 3)
Patients With Baseline Stamey = 1 (%)	24 (15.2%)	18 (13.1%)
Patients With Baseline Stamey = 2 (%)	59 (37.3%)	36 (26.3%)
Patients With Baseline Stamey = 3 (%)	75 (47.5%)	83 (60.6%)
Mean baseline pad weight in grams (Range)	74.8 (0.0 - 658.0)	85.3 (0.0 – 1267.0)
Mean baseline IQOL score (Range)	42.9 (3.0 - 90.0)	45.3 (2.0 - 88.0)

Treatment Information

Of the 296 patients receiving treatment, Stamey Grade evaluation at baseline as well as at the twelve-month period was available for 231 (131 Coaptite® and 100 Control) patients. Table 5 summarizes the treatment related data for the patients in both the Coaptite® and Control arms of the clinical study. A majority of the Coaptite® and Control patients received more than one injection. It was not uncommon for a 2nd and 3rd injection in both groups.

Table 5. Treatment Information for Patients followed for 12 Months

Treatment Information	Coaptite® N = 131	Control N = 100
Mean number of treatments per patient	1.9	2.0
Subjects receiving 1 treatment (%)	49 (37.4%)	27 (27.0%)
Subjects receiving 2 treatments (%)	51 (38.9%)	53 (53.0%)
Subjects receiving 3 treatments (%)	23 (17.6%)	15 (15.0%)
Subjects receiving > 3 treatments (%)	8 (6.1%)	5 (5.0%)

Treatment Information	Coaptite® N = 131	Control N = 100
Mean time between treatments (months)	2.8 (0.6 – 12.0)	2.7 (0.7 - 6.5)
Mean initial volume injected per patient (ml)	2.2 (0.5 - 4.5)	3.3 (1.0 - 7.5)
Mean total volume injected per patient (ml)	4.0 (1.0 - 11.0)	6.8 (1.5 - 19.5)

Effectiveness Results

Primary Effectiveness

The primary endpoint was to determine if Coaptite® was non-inferior to the Control in terms of the proportion of patients who experienced improvement (at least a one grade improvement on the Stamey Scale) and were able to maintain it twelve months after the initial injection treatment.

As shown in Table 6, there was no significant difference between Coaptite® and Control groups. Out of the 158 patients treated with Coaptite®, 91 improved and 15 had worsening of their incontinence. It was unclear whether the remaining 52 patients had any improvement from baseline.

Table 6. Intent-to-Treat (LOCF) 12-Month Effectiveness Results

EFFECTIVENESS at 12 MONTHS	Coaptite® N = 158	Control N = 138	p-value
STAMEY GRADE	# (%)	# (%)	
Dry (Grade 0)	54 (34.2%)	41 (29.7%)	0.4547
Substantially improved (≥ 2 grade decrease)	70 (44.3%)	53 (38.4%)	0.3446
Improvement (≥ 1 grade decrease)	91 (57.6%)	70 (50.7%)	0.2445
Worsening	15 (9.5%)	10 (7.2%)	0.5352
PAD WEIGHT			
Dry	37 (28.2%)	31 (31.0%)	0.8903
≥ 50% improvement	81 (51.3%)	53 (38.4%)	0.0547
1-49% improvement	12 (7.5%)	9 (6.5%)	
Worsening or no improvement from Baseline	65 (41.1%)	76 (55.1%)	
IQOL			
Mean improvement (range)	31.1 (-41.0 – +87.0)	25.9 (-44.0 – +91.0)	0.1340

Table 7 presents the effectiveness results for patients that completed the study. This table shows that, of the 131 Coaptite® treated patients who had 12-month Stamey Grade follow-up, 83 had improved and 13 had worsening of their incontinence from baseline. It is unclear whether the remaining 35 patients had any improvement in their incontinence.

Table 7. 12-Month Effectiveness Results for Pts with Complete 12- month Data

EFFECTIVENESS at 12 MONTHS	Coaptite®	Control	p-value
STAMEY GRADE	N = 131	N = 100	
Dry (Grade 0)	51 (38.9%)	37 (37.0%)	0.7859
Substantially improved (≥ 2 grade decrease)	66 (50.4%)	46 (46.0%)	0.5952
Improvement (≥ 1 grade decrease)	83 (63.4%)	57 (57.0%)	0.3441
Worsening or no improvement from Baseline	13 (9.9%)	6 (6.0%)	0.3393
PAD WEIGHT	N = 131	N = 99	
Dry	37 (28.2%)	31 (31.0%)	0.6625
$\geq 50\%$ improvement	81 (61.8%)	53 (53.5%)	0.3913
1-49% improvement	12 (9.2%)	9 (9.1%)	
Worsening or no improvement from Baseline	38 (29.0%)	37 (37.4%)	
IQOL	N = 123	N = 103	
Mean improvement (range)	31.1 (-41.0 – +87.0)	25.9 (-44.0 – +91.0)	0.1340

Table 8 provides effectiveness data with respect to the number of treatments patients received.

Table 8. Injection Results for the 12-month Completed Study

Effectiveness Results with respect to single vs multiple treatments	Coaptite® N = 131	Control N = 100
Improved at 12 months with single treatment	33/49 (67.4%)	21/27 (77.8%)
Cured at 12 months with single treatment	27/49 (55.1%)	17/27 (63.0%)
Improved at 12 months with multiple treatments	50/82 (61.0%)	36/73 (49.3%)
Cured at 12 months with multiple treatments	24/82 (29.3%)	20/73 (27.4%)

The route of injection, transurethral or periurethral, was at the discretion of the investigator. Table 9 provides details about the number of patients treated with transurethral or periurethral injection methods. Transurethral method was used in 92% of the Coaptite® patients and 89% of the control patients. There were insufficient numbers of patients treated by the periurethral method to determine the safety and effectiveness of this injection route for Coaptite®.

Table 9. Initial Route of Injection

Characteristic	Coaptite®	Control	p-Value
Route of Injection	158	138	0.5511
Transurethral	145 (91.8%)	123 (89.1%)	
Periurethral	13 (8.2%)	15 (10.9%)	

Secondary Effectiveness Results

Coaptite® was found to be not significantly different ($p = 0.7860$) to the Control in the proportion of patients who achieve and maintain a complete cure (Stamey Grade = 0) twelve months after the initial injection treatment (38.9% vs. 37.0%, respectively).

The proportion of Coaptite® patients who achieved and maintained substantial improvement (at least a two grade change or to Grade 0 at 12 months) was similar (p = 0.5952) to the Control patients (50.4% vs. 46.0%, respectively).

There was no significant difference (p = 0.2259) between Coaptite® patients that had at least a 50% decrease in pad weight at 12 months when compared to the Control patients (61.8% vs. 53.5%, respectively).

Patients were asked to complete an Incontinence Quality of Life Assessment (I-QOL). The results revealed that the patient's improvement in the quality of life score was similar for both groups (p = 0.1340) at the 12 month follow-up period when compared to the baseline score. Coaptite® demonstrated a significant improvement (p < 0.0001) in the quality of life score at 12 months when compared to the baseline score (see Table 10).

Table 10. Improvement in Quality of Life from Baseline at 12 Months

Category	Coaptite® N = 123	p-Value
Overall	31.1	< 0.0001
Avoidance and Limiting Behavior	31.3	< 0.0001
Psychosocial Impacts	27.6	< 0.0001
Social Embarrassment	35.9	< 0.0001

Safety Results

All Adverse Events Observed through 12 months

Safety of Coaptite® treatment was monitored by recording all adverse events (serious as well as non-serious) in the case report forms (CRFs). The CRF solicited a description of the event, start and stop dates, and its intensity, frequency, treatment, causality, and outcome. As expected, several patients were reported to have experienced adverse events in both Coaptite® and Control groups. The adverse event information reported included all the 158 Coaptite® treated patients and 138 Control treated patients. Overall, a total of 1265 adverse events were reported in both groups.

A total of 696 adverse events were reported during the study in the Coaptite® group, 17 serious adverse events (SAEs) and 679 non-serious adverse events (NSAEs). Some of the patients had both SAEs and NSAEs. In comparison, the control device had a total of 569 adverse events in 138 patients, 16 SAEs and 553 NSAEs. All the 16 SAEs in the control group occurred in 12 patients and were considered not related to the treatment (device or procedure). Only the NSAEs are discussed below. See Section VIII (Potential Adverse Effects) for a discussion of SAEs.

The patients in the Coaptite® and Control groups who had experienced the NSAEs (679 events in the Coaptite® group and 553 events in the Control group) are shown in Table 11, organized by the adverse event category. The 679 NSAEs in the Coaptite® group was the sum of both Treatment Related and Not Treatment Related NSAEs. This table presents the number of patients who experienced at least one NSAE.

Table 11. Total Non-Serious Adverse Events-Incidences and Patients

EVENT	Incidence		Patients		
	Coaptite®	Control	Coaptite® N = 158	Control N = 138	p-value
RENAL/GENITOURINARY	236	178	104 (65.8%)	91 (65.9%)	1.0
INFECTION, URINARY	75	72	46 (29.1%)	35 (25.4%)	0.51
PAIN, URINARY	55	27	30 (19.0%)	23 (16.7%)	0.65
SYNDROME	32	35	27 (17.1%)	21 (15.2%)	0.75
SEXUAL/REPRODUCTIVE FUNCTION	34	20	24 (15.2%)	16 (11.6%)	0.40
PAIN, NON URINARY	26	32	22 (13.9%)	25 (18.1%)	0.34
MUSCULOSKELETAL/SOFT TISSUE	27	20	21 (13.3%)	14 (10.0%)	0.47
GASTROINTESTINAL	33	30	21 (13.3%)	20 (14.5%)	0.87
INFECTION, NON URINARY	28	26	19 (12.0%)	20 (14.5%)	0.61
DERMATOLOGY/SKIN	25	14	14 (8.9%)	13 (9.4%)	1.0
METABOLIC/LABORATORY	20	22	14 (8.9%)	15 (10.9%)	0.56
SURGERY/INTRA-OPERATIVE INJURY	14	8	13 (8.2%)	7 (5.1%)	0.36
LYMPHATICS	11	8	11 (7.0%)	8 (5.8%)	0.81
NEUROLOGY	12	15	10 (6.3%)	12 (8.7%)	0.51
PULMONARY/UPPER RESPIRATORY	13	15	9 (5.7%)	12 (8.7%)	0.37
VASCULAR	10	4	9 (5.7%)	3 (2.2%)	0.15
ALLERGY/IMMUNOLOGY	7	4	7 (4.4%)	4 (2.9%)	0.55
BLOOD/BONE MARROW	7	7	7 (4.4%)	4 (2.9%)	0.55
ENDOCRINE	5	4	5 (3.2%)	4 (2.9%)	1.0
CARDIAC GENERAL	5	1	4 (2.5%)	1 (0.7%)	0.38
CARDIAC ARRHYHMIA	3	2	2 (1.3%)	2 (1.4%)	1.0
OCULAR/VISUAL	1	6	1 (0.6%)	5 (3.6%)	0.10
AUDITORY/EAR	0	2	0 (0.0%)	2 (1.4%)	0.22
HEPATOBIILIARY/PANCREAS	0	1	0 (0.0%)	1 (0.7%)	0.47
TOTAL Non-Serious Adverse Events	679	553	-	-	-

The p-values provided in Table 11 show that the number of patients who experienced the NSAEs in each adverse event category was similar in both Coaptite® and Control groups and there is no statistically significant difference between the two groups.

Although there are additional potential risks with bulking agents identified in the literature, including hardening of the tissues at the injection site and/or allergic or autoimmune reactions, these were not reported in any patients.

Treatment Related Adverse Events

Of the 679 total NSAEs in the Coaptite® group, 334 NSAEs were determined to be treatment related. They occurred in 137 Coaptite® patients. The corresponding number of treatment related NSAEs in the Control group were 257. The criteria used for determining that an adverse event was related to the treatment are described on the following page:

- NSAE occurring 0 to 7 days after any injection,
- NSAE occurring >7days after any injection and considered definitely related to the injection,
- NSAE occurring > 7 days after any injection and considered probably related to the injection,
- NSAE occurring > 7 days after any injection and unknown if it was related to the injection.

These were conservative criteria for determining whether a NSAE was treatment related. Table 12 presents the number of **treatment related** incidence and patients in both treatment groups with a NSAE in each adverse event category.

Table 12. Treatment Related Non-Serious Adverse Events-Incidence and Patients

EVENT	Incidence		Patients		
	Coaptite®	Control	Coaptite® N = 158	Control N = 138	p-value
RENAL/GENITOURINARY	196	142	95 (60.1%)	81 (58.7%)	0.8135
PAIN, URINARY	42	21	27 (17.1%)	18 (13.0%)	0.4175
INFECTION, URINARY	19	24	14 (8.9%)	14 (10.1%)	0.8426
SURGERY/INTRA-OPERATIVE INJURY	11	7	11 ((7.0%)	6 (4.3%)	0.4541
SEXUAL/REPRODUCTIVE FUNCTION	10	8	10 (6.3%)	8 (5.8%)	1.0000
GASTROINTESTINAL	13	7	10 (6.3%)	6 (4.3%)	0.6080
PAIN, NON URINARY	7	11	7 (4.4%)	11 (8.0%)	0.2298
SYNDROME	6	3	5 (3.2%)	3 (2.2%)	0.7279
DERMATOLOGY/SKIN	8	2	5 (3.2%)	2 (1.5%)	0.4551
LYMPHATICS	5	3	5 (3.2%)	3 (2.2%)	0.7279
INFECTION, NON URINARY	7	8	4 (2.5%)	8 (5.8%)	0.2369
MUSCULOSKELETAL/SOFT TISSUE	3	1	3 (1.9%)	1 (0.7%)	0.6259
NEUROLOGY	2	3	2 (1.3%)	3 (2.2%)	0.6669
VASCULAR	3	0	2 (1.3%)	0 (0.0%)	N/A
METABOLIC/LABORATORY	1	2	1 (0.6%)	1 (0.7%)	1.0000
CARDIAC ARRHYHMIA	1	0	1 (0.6%)	0 (0.0%)	N/A
ALLERGY/IMMUNOLOGY	0	3	0 (0.0%)	3 (2.2%)	N/A
BLOOD/BONE MARROW	0	5	0 (0.0%)	3 (2.2%)	N/A
ENDOCRINE	0	1	0 (0.0%)	1 (0.7%)	N/A
PULMONARY/UPPER RESPIRATORY	0	3	0 (0.0%)	3 (2.2%)	N/A
OCULAR/VISUAL	0	2	0 (0.0%)	2 (1.5%)	N/A
CARDIAC GENERAL	0	1	0 (0.0%)	1 (0.7%)	N/A
AUDITORY/EAR	0	0	0 (0.0%)	0 (0.0%)	N/A
HEPATOBIILIARY/PANCREAS	0	0	0 (0.0%)	0 (0.0%)	N/A
TOTAL Non-Serious Adverse Events	334	257	101 (63.9%)	91 (65.9%)	0.8073

The table shows that the Coaptite® and Control groups had similar rates of **treatment related** adverse events in each adverse event category and there was no statistically significant difference between the two groups. Coaptite® group had no allergic or immunologic reactions while 3 patients had allergic reactions in the Contigen group. Urinary tract infection (UTI), a common occurrence with urological procedures, occurred in both Coaptite® and Control groups at the

same rate. Thirteen (13) Coaptite® patients had 18 UTIs as compared to 14 Control patients with 24 UTIs.

Urinary retention had the highest rate among the genitourinary NSAEs. Forty one percent (41%) of the Coaptite® patients and 33% of Control patients had urinary retention related to the treatment. Retention is followed by hematuria (19.6%) and dysuria (15%) in Coaptite® patients.

Most **treatment related** adverse events occurred within 24 hours of treatment and subsequently resolved within 30 days. At the time of database closure, 91% of treatment related adverse events were resolved. The following treatment related urinary related events were persistent or resolution was unconfirmed at the time of database closure (the number of events is shown in parentheses): Urge incontinence (5); micturition urgency (3); hypertonic bladder (2); urinary retention (2); urethral disorder (2); and one event each of back pain, bladder spasm, dysuria, injection site reaction, mucosal erosion, edema peripheral, urinary tract obstruction.

With respect to severity of the 334 **treatment related** adverse events in the Coaptite® group:

- 232 (69.5%) were rated as mild;
- 92 (27.6%) were rated as moderate; and
- 10 (3.0%) were rated as severe.

Adverse Events Reported Between 12 and 24 Month Follow-up

A total of 11 adverse events were reported between 12 and 24 months for the 48 COAPTITE® patients seen through 24 months. One serious adverse event was reported (bladder cancer) and determined not to be related to either the procedure or the device. The remaining non-serious adverse events reported between 12 and 24 months include hematuria (1), inflamed introitus (1), anterior bladder neck swelling (1), urinary tract infection (4), urge incontinence (1), bladder erythema (1), and burning on urination (1).

XI. CONCLUSIONS

The preclinical data provided, adequately characterize the device's materials, justify a 3-year shelf life and demonstrate that Coaptite® is safe for long-term implantation in the urethral submucosa.

The results of the study on all treated patients (158 in Coaptite® group and 138 in the Control group) demonstrate that 34% of the Coaptite® patients were dry and 57.6% were improved by Stamey Grade assessment. In comparison, 30% of the Control patients achieved dryness and 51% achieved improvement. Using the criteria of 24-hour pad weight results, 28% achieved dryness and 51% achieved improvement ($\geq 50\%$ decrease in urine loss after treatment) in the Coaptite® group. Comparative cure and improvement rates were 31% and 38% respectively for the Control.

The statistical analyses (p-values) clearly demonstrate that Coaptite® is non-inferior to the Control for soft tissue augmentation for the treatment of SUI. The quality of life for all patients (both Coaptite® and Control patients) revealed a

significant improvement when comparing the 12-month scores to the baseline scores.

There were two **unanticipated, treatment related, serious adverse effects** in the Coaptite® group. These SAEs involved dissection of the device through tissue resulting in tissue bridges and erosion. Upon review of these events, it could not be concluded whether they were directly attributable to the device; the events were believed to be more likely the result of poor injection technique. Another consideration is that peripheral vascular disease and prior pelvic surgery could have contributed to the tissue erosion. The boxed warnings in the physician labeling (Instructions for Use) are intended to alert the physicians to the consequences of a poor injection technique and improper patient selection, and minimize the chances of occurrence of similar types of adverse events in the future. The postmarket enhanced surveillance and postapproval study requirements are intended to help identify the cause of these adverse events, should they occur again.

With regard to anticipated adverse effects Coaptite® had a safety profile similar to that of the Control. Furthermore, Coaptite® did not have any incidence of treatment related allergic reactions as compared to the Control which had allergic cases. None of the subjects experienced prolonged retention, obstruction, nor complaints of prolonged pain, discomfort, or inflammation in the area of the implant were reported. There were no clinically significant laboratory findings that indicated Coaptite® exhibited any systemic effects.

It has been concluded that Coaptite® is safe and effective for its intended use of soft tissue augmentation of the urethral sphincter in the treatment of stress urinary incontinence when it is used in accordance with the Instructions for Use.

XII. PANEL RECOMMENDATIONS

In accordance with the provisions of section 515(c)(2) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Gastroenterology and Urology Devices Advisory Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XIII. CDRH DECISION

CDRH has reviewed the **two serious, treatment related adverse events** in Coaptite® injected patients and required boxed warnings to alert physicians to the potential occurrence of similar events in the future. This step for physician awareness is intended to help minimize the incidence of this type of adverse event when Coaptite® is marketed. One of the conditions of approval is a 2-year enhanced postmarket surveillance program that requires the company to actively solicit the adverse event information related to the use of Coaptite®. This requirement would help in documenting the rate of occurrence of similar serious adverse events. Another requirement, a 5-year postapproval study, would help in establishing the causality of these serious adverse events, if they occur in the future.

Based upon its review of the PMA, CDRH concludes that these data, the labeling requirements and postapproval requirements provide a reasonable assurance that Coaptite® is safe and effective when used in accordance with the Instructions for Use.

FDA issued an approval order on November 10, 2005

The applicant's manufacturing facility was inspected on June 14-17, 2004, and was found to be in compliance with the Quality System Regulation (21 CFR 820).

XIV. APPROVAL SPECIFICATIONS

Instructions for Use: See the labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions and Adverse Events in the labeling.

Post-approval Requirements and Restrictions: See approval order.

XV. REFERENCES

1. Use of International Standard ISO 1099'3-1, 'Biological Evaluation of Medical Devices, Part I: Evaluation and Testing." FDA, CDRH, May 1, 1995.
2. Stamey T. Urinary Incontinence in the Female: In Campbell's Urology. Fourth Edition. Philadelphia. W.B. Saunders Company. pp. 2272-2293. 1979.