

INSTRUCTIONS FOR USE

CAUTION: Federal law (USA) restricts this device to sale by or on the order of a physician trained in diagnostic and therapeutic cystoscopy.

DESCRIPTION

Coaptite® is an injectable, sterile, non-pyrogenic implant composed of spherical particles of calcium hydroxylapatite (CaHA) particles (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.

MODE OF ACTION

Coaptite® is injected sub-mucosally at the bladder neck. The injection of Coaptite® creates increased tissue bulk and soft tissue augmentation of the bladder neck and/or urethra. The gel carrier suspends the CaHA particles and allows delivery through injection needles and is dissipated *in vivo*, while the CaHA particles remain at the injection sites and provide the tissue bulking to cause coaptation of the urethra and increase urethral resistance to urine leakage.

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.

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.

WARNING: Following injection of Coaptite®, dissection of the device through tissue may lead to 1) tissue erosion and may require corrective surgery or 2) elevation of the bladder wall causing ureteral obstruction. This may be caused by improper injection technique using Coaptite®. (See adverse event section on page 3 for further information)

WARNING: Women with peripheral vascular disease and prior pelvic surgery may be at increased risk for tissue erosion following injection of Coaptite®. (See adverse event section on page 3 for further information)

WARNINGS

- Coaptite® in patients with urethral or bladder neck strictures should not be used until the strictures have been corrected. Use of Coaptite® in patients with strictures may cause injury and/or urethral obstruction.

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- Avoid using Coaptite® in patients with non-viable tissue, e.g., history of significant pelvic irradiation, multiple pelvic surgeries, etc. Scar tissue and significantly compromised tissue will not coapt appropriately.
- Avoid using Coaptite® in patients with very short urethras and who have had multiple surgeries for stress incontinence. These patients may experience urethral caruncle formation.
- Over correction using Coaptite® may lead to obstruction.
- Avoid injecting Coaptite® in blood vessels. Coaptite® injection into blood vessels may cause vascular occlusion.
- Injections of Coaptite® should only be performed by physicians who have experience with diagnostic and therapeutic cystoscopic procedures.

PRECAUTIONS

- The long-term safety and effectiveness of Coaptite® treatment has not been established.
- Safety and effectiveness of periurethral injection of Coaptite® has not been established.
- Safety and effectiveness of Coaptite® in men has not been established.
- Safety and effectiveness of Coaptite® in patients with the following conditions has not been established.
 - Urinary incontinence due to detrusor instability
 - Bladder neuropathy
 - Nocturnal enuresis (bed wetting)
 - Prolapsed bladder
 - Overflow incontinence
 - Functional incontinence
- Safety and effectiveness of Coaptite® in patients that are pregnant or lactating has not been established.
- The effect of Coaptite® on subsequent pregnancy and delivery, and the impact of subsequent pregnancy on the effect of Coaptite®, is unknown. Therefore, the risks and benefits of the device in women of childbearing potential should be carefully assessed.
- Patients should be counseled that one or more repeat Coaptite® injection procedures may be required to achieve dryness or a satisfactory level of improvement in urinary incontinence.
- **Do not re-sterilize.** Coaptite® is supplied sterile and non-pyrogenic in a sealed foil pouch and is intended for single use only. The foil pouch should be carefully examined to verify that neither the pouch nor the Coaptite® syringe has been damaged during shipment.
- **Do not use** if the foil pouch is compromised or the syringe has been damaged.
- **Do not use** if the syringe end cap or syringe plunger are not in place or removed.

ADVERSE EVENTS

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 158 Coaptite® and 138 control patients. Of those adverse events a total of 33 were serious adverse events (SAE) in 11 Coaptite® and

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12 Control patients. There was one death of a patient that was injected with Coaptite® (lung cancer) reported in the study, but was determined not to be treatment related.

Unanticipated Device Related Adverse Effects

There were **two serious adverse events** in the Coaptite® group (1.3%) involving erosion and were determined to be treatment related.

- One patient with peripheral vascular disease experienced erosion of approximately 1 cm on the anterior vaginal wall just proximal to the meatus. 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 is no longer connected to the underlying structures and required corrective surgery.
- The 2nd patient with a history of prior pelvic surgeries 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 surgical intervention was required.

Other Device Related Adverse Effects

A total of 334 non-serious **treatment related** adverse events were reported in the Coaptite® group in 137 patients. 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.

Table 1 below presents information on patients who experienced genitourinary adverse events. The adverse events were treatment-related, non-serious adverse events.

Table 1
Genitourinary Treatment Related Non-Serious Adverse Events

| TYPE OF EVENT | Coaptite® SUBJECTS N=158 | | |
|-------------------------|-----------------------------|------------|------------|
| | No. Patients | % Patients | No. Events |
| Urinary Retention | 65 | 41.1% | 99 |
| Hematuria | 31 | 19.6% | 48 |
| Dysuria | 24 | 15.2% | 32 |
| UTI | 13 | 8.3% | 18 |
| Urinary Urgency | 12 | 7.6% | 14 |
| Urinary Frequency | 11 | 7.0% | 12 |
| Urge Incontinence | 9 | 5.7% | 9 |
| Injection Site Pain | 3 | 1.9% | 4 |
| Genitourinary Infection | 2 | 1.3% | 2 |
| Erosion | 2 | 1.3% | 2 |
| Urine Analysis Abnormal | 2 | 1.3% | 3 |
| Pelvic Pain | 1 | 0.6% | 1 |

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): Worsening of Incontinence (5); Urinary 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.

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).

CLINICAL STUDY

Purpose of Study

The objective was to evaluate the safety and effectiveness of Coaptite® compared to a commercially available bulking agent (Control) in adult female patients with SUI due to ISD and without associated urethral hypermobility.

Study Design

The study was a prospective, randomized, multi-center, single blind, comparative parallel, clinical trial of Coaptite® and Control for soft tissue augmentation in the patients specified above.

Primary Effectiveness Endpoint

The primary effectiveness endpoint was to determine if in adult females with SUI due

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to ISD, 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. Stamey Grade was used to measure patient improvement and success was defined as a decrease of at least one continence grade at 12 months from baseline. The Stamey Grade was based on a scale with the following designations:

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.

Patient continence status was evaluated prior to treatment (Baseline) and at 6 months and 12 months after the initial injection.

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 Endpoint

Safety was evaluated by the number and duration of device or procedure related adverse events, as assessed by severity and causality including infection, obstruction, pain and discomfort, as well as laboratory evaluations.

Patients Accountability, Baseline and Treatment Information

A total of 545 patients consented. 249 patients did not undergo treatment due to failed screening, withdrawal of consent prior to treatment or other reasons. 296 patients were injected with either Coaptite® (158 patients) or Control (138 patients). All patients were ≥ 21 years of age.

**Table 3
Patient Accountability**

| CLINICAL STUDY PATIENT ACCOUNTABILITY | Coaptite® | CONTROL |
|--|------------------|----------------|
| Number of subjects treated | 158 | 138 |
| Number of subjects with 12-month follow-up after initial treatment | 131 | 100 |
| Number of subjects with 24-month follow-up after initial treatment | 48 | - |

**Table 4
Patient Baseline Profile**

| | Coaptite® N = 158 | CONTROL N = 138 |
|---|------------------------------|----------------------------|
| Mean Age (range) | 61.1 | 60.5 |
| Mean Duration of Incontinence (Years) | 10.2 | 9.2 |
| Mean Baseline Stamey Grade | 2.3 | 2.5 |
| 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) |

**Table 5
Treatment Information**

| FOR SUBJECTS FOLLOWED FOR 12 MONTHS | 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%) |
| Mean time between treatments in months (range) | 2.8 (0.6 - 12.0) | 2.7 (0.7 - 6.5) |
| Mean initial volume injected per patient in ml (range) | 2.2 (0.5 - 4.5) | 3.3 (1.0 - 7.5) |
| Mean total volume injected per patient in ml (range) | 4.0 (1.0 - 11.0) | 6.8 (1.5 - 19.5) |

Effectiveness Results at 12 Months

There was no statistically significant difference in the effectiveness of Coaptite® compared to the Control. The data was analyzed on the intent-to-treat patient population imputing last observation carried forward (LOCF) for all missing values. Data is also presented using only the evaluable patient population by removing the data from the analysis where patients were lost or withdrew from the study before completing the 12-month follow-up.

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

| EFFECTIVENESS at 12 MONTHS | Coaptite® N = 158 | CONTROL N = 138 |
|---|------------------------------|----------------------------|
| STAMEY GRADE | # (%) | # (%) |
| Dry (Grade 0) | 54 (34.2%) | 41 (29.7%) |
| Substantially improved (≥ 2 grade decrease) | 70 (44.3%) | 53 (38.4%) |
| Improvement (≥ 1 grade decrease) | 91 (57.6%) | 70 (50.7%) |
| Worsening or no improvement from Baseline | 15 (9.5%) | 10 (7.2%) |
| PAD WEIGHT | | |
| Dry | 37 (28.2%) | 31 (31.0%) |
| ≥ 50% improvement | 81 (51.3%) | 53 (38.4%) |
| 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) |

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

| EFFECTIVENESS at 12 MONTHS | Coaptite® | CONTROL |
|---|-------------------------|-------------------------|
| STAMEY GRADE | N = 131 | N = 100 |
| Dry (Grade 0) | 51 (38.9%) | 37 (37.0%) |
| Substantially improved (≥ 2 grade decrease) | 66 (50.4%) | 46 (46.0%) |
| Improvement (≥ 1 grade decrease) | 83 (63.4%) | 57 (57.0%) |
| Worsening or no improvement from Baseline | 13 (9.9%) | 6 (6.0%) |
| PAD WEIGHT | N = 131 | N = 99 |
| Dry | 37 (28.2%) | 31 (31.0%) |
| ≥ 50% improvement | 81 (61.8%) | 53 (53.5%) |
| 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) |

24-month follow-up Stamey Grade data was available on 39 patients where 12 of those patients remained dry at 24 months and 26 remained improved with at least one grade decrease from baseline using Stamey Grade.

PHYSICIAN TRAINING

To use Coaptite®, physicians must have training in diagnostic and therapeutic cystoscopy.

Patient Counseling

Prior to Coaptite® therapy, the risks and benefits associated with Coaptite® and urethral bulking procedures should be thoroughly discussed with the patient. The

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patient should be fully apprised of the indications, contraindications, warnings, precautions, expected clinical outcomes, adverse events, and method of implantation. The patient should be advised that bulking agent therapy with Coaptite® is a course of treatment that may require more than one injection procedure to achieve dryness or a desired level of improvement in incontinence. Patients should be counseled to report adverse events to the treating physician. Physicians should report device-related adverse events to BioForm Medical, Inc. toll-free (866) 862-1211. The Patient Information Brochure may be beneficial in providing additional information to the patient.

Patients should be advised that they may experience transient, discomfort or dysuria following the procedure and a small number may also experience discomfort during sexual intercourse or detrusor instability.

DIRECTIONS FOR USE

The following is required for a transurethral injection of Coaptite®:

- 35cm cystoscopic injection needle with a 10mm, 21 gauge needle tip.
- Cystoscope with a larger than 5 or 7 Fr working channel

Operative Preparation:

Place the patient in the lithotomy position, anesthetize, and prepare for surgery using standard operative procedures. Coaptite® may be injected using local, regional, or general anesthesia.

1. Remove foil pouch from the shipping box. The pouch can be opened and the syringe of Coaptite® dropped onto the sterile field when required.
Note: There is a small amount of moisture normally present inside the foil pouch for sterilization purposes; this is not an indication of a defective product.
2. Prepare the syringes of Coaptite®, injection needle(s), and cystoscopic equipment before the surgical injection. A new injection needle may be used for each syringe or the same injection needle may be connected to each new syringe. **In all circumstances, when the injection needle is attached to the syringe of Coaptite®, the needle must be tightened securely to the syringe. Prime the needle with Coaptite®.** Prepare cystoscopic equipment according to manufacturer's Instructions for Use.
3. The urethra and bladder neck should be examined prior to injection.

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WARNING: Women with peripheral vascular disease and prior pelvic surgery may be at increased risk for tissue erosion following injection of Coaptite®. (See adverse event section on page 3 for further information)

4. Remove the Luer syringe cap (on the distal end of the syringe) prior to attaching the injection needle. If excess Coaptite® is on the surface of the Luer lock fittings, it will need to be wiped clean with sterile gauze. The syringe of Coaptite® can then be twisted onto the Luer lock fitting of the injection needle. **The injection needle must be tightened securely to the syringe.** Slowly push the syringe plunger until Coaptite® extrudes from end of the injection needle. If leakage is noted at the Luer fitting, it may be necessary to remove the injection needle and clean the surfaces of the Luer fitting or in extreme cases, replace both the syringe and the injection needle.
5. The injection needle is then advanced through the working channel of the cystoscope. A desired location for the SUI injection into the urethra or bladder neck needs to be identified. This is usually 1 to 1.5 centimeters distal to the bladder neck. Push the injection needle into the submucosal lining of the urethra at the desired site. Slowly push the plunger shaft of the Coaptite® syringe to start the injection. Some tissue planes may be difficult to inject. If significant resistance is encountered when pushing the plunger shaft, the injection needle should be pulled back about 1-3 millimeters (with the needle still in the urethral tissue) and push the plunger shaft slowly again. If significant resistance is still encountered, it may be necessary to pull the injection needle entirely out of the injection site, verify material injects out of the needle, and try again in a new position. If significant resistance continues to persist, it may be necessary to try a different injection needle. If the injection needle becomes kinked, bent or is damaged so as to restrict the flow of Coaptite®, the needle must be replaced.
6. When Coaptite® starts to flow into the injection site tissue bulking in the form of a bleb should be visible. If it is not observable, pull back on the injection needle and locate the needle more superficially and begin injecting again. This site should be injected until the bleb meets the midline of the urethra or maximum tissue compliance. Further injection may extravasate or rupture the site. Additional sites should be injected until the urethral opening has coapted or closed off. Avoid over correction as urinary retention may occur.
7. Multiple syringes may be required to coapt the urethra. In the clinical study, the average initial treatment was 2.2 cc of Coaptite®, with the average total volume being 4.0 cc of Coaptite®. The injection needle already in place may be used with each new syringe of Coaptite® or a new injection needle may

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be used. Regardless, be certain there is no Coaptite® present at the connections prior to attachment. **If a new injection needle is used, the needle must be tightened securely to the syringe. Prime the needle with Coaptite® prior to insertion into the cystoscope.**

8. After the injections have been completed, it is important not to pass the cystoscope through the coaptation site as this may deform the tissue blebs that have been formed.
9. Prior to discharge, the patient must be able to void freely. In case of urinary retention, intermittent catheterization (12 Fr or smaller) is recommended until normal voiding resumes.
10. Used and partially used syringes and used injection needles could be biohazardous and should be handled and disposed of in accordance with facility medical practices and local, state or federal regulations.

HOW SUPPLIED

Coaptite® is a sterile, non-pyrogenic bulking agent, supplied in single use, latex-free, 1.0 cc syringe. The syringe is packaged in a foil pouch. The pouch is boxed and individually shrink wrapped.

Upon receipt of shipment, check the packaging to ensure that the packaging is intact and there has been no damage from shipment.

The contents of the syringe are intended for single patient use only and cannot be re-sterilized.

SHELF LIFE AND STORAGE

Coaptite® should be stored at a controlled room temperature (15°C - 32°C: 59°F - 90°F). The expiration date, when stored in these temperatures, is three years from date of manufacture. Do not use if the expiration date has been exceeded. Do not resterilize. Do not use if package is opened or damaged.

WARRANTY

BioForm Medical, Inc. warrants that reasonable care has been exercised in the design and manufacture of this product.

THIS WARRANTY IS IN LIEU OF AND EXCLUDES ALL OTHER WARRANTIES NOT EXPRESSLY SET FORTH HEREIN, WHETHER EXPRESSED OR IMPLIED BY OPERATION OF LAW OR OTHERWISE, INCLUDING BUT NOT LIMITED TO, ANY IMPLIED WARRANTIES OF MERCHANTABILITY OR FITNESS FOR ITS PARTICULAR PURPOSE.

Handling and storage of this product, as well as factors relating to the patient, diagnosis, treatment, surgical procedures and other matters beyond BioForm Medical's control directly affect the product and the results obtained from its use. BioForm Medical's obligation under this warranty is limited to the replacement of this

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product and BioForm Medical shall not be liable for any incidental or consequential loss, damage, or expense, directly or indirectly, arising from the use of this product. BioForm Medical neither assumes, nor authorizes any person to assume for BioForm Medical, any other or additional liability or responsibility in connection with this product.

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