Coaptite®

INJECTABLE IMPLANT
INSTRUCTIONS FOR USE

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

DEVICE DESCRIPTION

The COAPTITE® Injectable Implant 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.

INTENDED USE

The COAPTITE® Injectable Implant is injected sub-mucosally at the bladder neck. The injection 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

The COAPTITE® Injectable Implant 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 the COAPTITE® Injectable Implant, 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 the COAPTITE® Injectable Implant. (See POST-APPROVAL STUDY section for further information.)
WARNING: Women with peripheral vascular disease and prior pelvic surgery may be at increased risk for tissue erosion following injection of the COAPTITE® Injectable Implant. (See POST-APPROVAL STUDY section for further information.)

WARNINGS

- The COAPTITE® Injectable Implant in patients with urethral or bladder neck strictures should not be used until the strictures have been corrected. Use in patients with strictures may cause injury and/or urethral obstruction.
- Avoid using 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 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 the COAPTITE® Injectable Implant may lead to obstruction.
- Avoid injecting in blood vessels. The COAPTITE® Injectable Implant injection into blood vessels may cause vascular occlusion.
- Injections of the COAPTITE® Injectable Implant should only be performed by physicians who have experience with diagnostic and therapeutic cystoscopic procedures.

PRECAUTIONS

- The long-term safety and effectiveness of the COAPTITE® Injectable Implant treatment has not been established.
- Safety and effectiveness of periurethral injection of the COAPTITE® Injectable Implant has not been established.
- Safety and effectiveness of the COAPTITE® Injectable Implant in patients under the age of 18 and men has not been established.
- Safety and effectiveness of the COAPTITE® Injectable Implant 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
  - Diabetes
  - Immunosuppressive Disorders
- Safety and effectiveness of the COAPTITE® Injectable Implant in patients that are pregnant or lactating has not been established.
- The effect of the COAPTITE® Injectable Implant on subsequent pregnancy and delivery, and the impact of subsequent pregnancy on the effect of the COAPTITE® Injectable Implant, is unknown. Therefore, the risks and benefits of the implant in women of childbearing potential should be carefully assessed.
- Patients should be counseled that one or more repeat injection procedures may be required to achieve dryness or a satisfactory level of improvement in urinary incontinence.
- **Do not re-sterilize.** The COAPTITE® Injectable Implant 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 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.

POST-APPROVAL STUDY

Summary of the Post-Approval Study Methods

Study Objective

The primary safety objective of the study is to assess the long-term safety of calcium hydroxylapatite suspended in gel (COAPTITE® Injectable Implant), specifically tissue erosion, dissection, and material migration.

The primary effectiveness objective of the study is to assess long term durability of COAPTITE® Injectable Implant.

Study Population

A total of 459 females with a diagnosis of stress urinary incontinence due to intrinsic sphincter deficiency were enrolled in 20 investigative sites throughout the United States.

Study Design

This single arm, multi-center, open label, 36-month post market study of COAPTITE® Injectable Implant was designed to assess the long-term safety and effectiveness of COAPTITE® Injectable Implant in the treatment of female urinary incontinence. Subjects were administered an initial injection of COAPTITE® Injectable Implant within 60 days of pad weight confirmation. Additional injections were administered at any study visit as clinically indicated. Subjects were to return for a cystoscopy 1 month after each of the two injections administered within six months of the enrollment.

Study Visits and Length of Follow-up

Subjects were followed for 36 months with visits at 6, 12, 18, 24, 30 and 36 months after their initial injection.

Key Study Endpoints

Safety assessments included assessing for tissue erosion, dissection, material migration and the overall adverse event (AE) profile. A local periurethral exam was performed at all study follow-up visits and a cystoscopy was performed after the first two COAPTITE® Injectable Implant injections (administered within the first six months of treatment). AEs were captured routinely throughout the duration of the study.

The primary effectiveness assessment was based on the changes from baseline in Stamey Grading Score over time. Effectiveness assessments included the number of COAPTITE® Injectable Implant injections, need for alternative treatments, urge incontinence medication usage, and the Incontinence Quality of Life (iQoL) questionnaire.

Summary of Post-Approval Study Results

Safety Finding

Among the 459 subjects treated, 313/459 (68.2%) experienced at least one Treatment Emergent Adverse Event (TEAE) for a total of 1116 Adverse Events (AEs) reported (see Table 1). The majority of the TEAEs subjects experienced during the study were either mild (n = 175/459; 38.1%) or moderate (n = 92/459; 20%) TEAEs and determined to be not related to treatment (n = 219/459; 47.7%).

Table 1 Overall Summary of Treatment Emergent Adverse Events (N = 459)

		Number of Subjects	%
Number of subjects with a TEAE	Any TEAE	313	68.2
Max. Intensity of TEAEs	Mild	175	38.1
	Moderate	92	20
	Severe	46	10
Worst Causality of TEAEs	Related	94	20.5
	Not Related	219	47.7

TEAE = treatment emergent adverse event

When comparing safety results for completers and non-completers, the results were consistent with one another and as a result the safety profile was not influenced by whether or not a subject completed the study.

Note Regarding Adverse Events

Although not observed in the COAPTITE® clinical study, the following adverse events/complications have been reported with the use of urethral bulking agents, some of which may occur with COAPTITE® use: pain, swelling/oedema, erythema, granuloma, abscess formation, scarring, fistula formation, fibrosis, necrosis, hypersensitivity and/or allergic reactions, calcifications, calculus formations, embolic phenomena, sepsis, and material migration/discharge.

All Adverse Events

The total number of subjects with at least one TEAE with an incidence of ≥ 5% was 246/459 (53.6%). These 246 subjects experienced a total of 496 events (see Table 2).

Within the renal and urinary disorders System Organ Class (SOC), 176 (38.3%) subjects of the total population (N = 459) contributed to a total of 231 events (126 events of urge incontinence, 76 events of urinary retention, and 29 events of micturition urgency). Within the infections and infestations SOC, 136 (29.6%) subjects of the total population (N = 459) contributed to a total of 265 events, all of which were urinary tract infections.

Table 2 Number (%) of Subjects with Treatment Emergent Adverse Events by System Organ Class and Preferred Term Reported with an Incidence of ≥ 5% (N=459)

System Organ Class Preferred Term	Number of Subjects	%	Number of Events
Subjects with at least one TEAE	246	53.6	496
Renal and Urinary Disorders	176	38.3	231
Urge Incontinence	109	23.7	126
Urinary Retention	66	14.4	76
Micturition Urgency	29	6.3	29
Infections and Infestations	136	29.6	265
Urinary Tract Infections	136	29.6	265

TEAE = treatment emergent adverse event

Relationship to Treatment

The majority of TEAEs were not related to treatment; there were 219/459 (47.7%) subjects with not related TEAEs compared with 94/459 (20.5%) of subjects with related TEAEs. The most common TEAE reported as related to treatment was urinary retention (see Table 3).

Table 3 Number (%) of Subjects with Treatment Emergent Adverse Events by Relationship to Treatment Reported with an Incidence of ≥ 5% (N=459)

System Organ Class Preferred Term	Related		Not Related	
	Number of Subjects	%	Number of Subjects	%
Subjects with at least one TEAE	94	20.5	219	47.7
Renal and Urinary Disorders	69	15	128	27.9
Urinary Retention	60	13.1	6	1.3
Urge Incontinence	8	1.7	101	22
Micturition Urgency	4	0.9	25	5.4
Infections and Infestations	13	2.8	146	31.8
Urinary Tract Infections	13	2.8	123	26.8

TEAE = treatment emergent adverse event

Serious Adverse Events (SAEs)

Of the 163 subjects with SAEs reported, 52 subjects experienced SAEs that were considered to be related, probably related, or possibly related to treatment and 95 subjects experienced SAEs that were considered not related or unlikely related to treatment. The causality was unknown for 16 subjects (see Table 4).

Table 4 Overall Summary of Serious Adverse Events (N=459)			
		Number of Subjects	%
Number of Subjects with a Serious TEAE	Any Serious TEAE	163	35.5
Worst Causality of Serious TEAEs	Related	42	9.2
	Probable	2	0.4
	Possible	8	1.7
	Unlikely	2	0.4
	Not Related	93	20.3
	Unknown	16	3.5

TEAE = treatment emergent adverse event

There were a total of 356 SAEs experienced by these 163 subjects. The majority of the serious TEAEs were urinary tract infection 187/356 in the infections and infestations SOC and urinary retention 70/356 in the renal and urinary disorders SOC (see Table 5).

Table 5 Number (%) of Subjects with Serious Treatment-Emergent Adverse Events and Number of Serious Treatment-Emergent Adverse Events ≥ 2 Events by System Organ Class and Preferred Term (N=459)			
System Organ Class Preferred Term	Number of Subjects	%	Number of Events
Subjects with at least one TEAE	163	35.5	356
Infections and Infestations	120	26.1	209
Urinary Tract Infection	114	24.8	187
Fungal Infection	5	1.1	5
Cystitis	4	0.9	4
Vulvovaginal Mycotic Infection	2	0.4	2
Renal and Urinary Disorders	88	19.2	120
Urinary Retention	63	13.7	70
Urge Incontinence	27	5.9	28
Micturition Urgency	4	0.9	4
Pollakiuria	4	0.9	4
Haematuria	3	0.7	3
Nocturia	2	0.4	2
Urethritis noninfective	2	0.4	2
Haemorrhage Urinary Tract	1	0.2	2
Reproductive System and Breast Disorders	4	0.9	5
Cystocele	2	0.4	2
Vascular Disorders	1	0.2	2
Haemorrhage	1	0.2	2

TEAE = treatment emergent adverse event

Of the 163 subjects reporting serious TEAEs, there were 118/459 (25.7%) subjects with serious TEAEs considered not related to treatment compared with 55/459 (12.0%) subjects with serious TEAEs that were considered to be related to treatment. There were 35/459 (7.6%) of serious TEAEs for which the relationship was unknown. The most common Serious TEAE considered not related to treatment was urinary tract infection 98/459 (21.3%) in the infections and infestations SOC; the most common serious TEAE considered related to treatment was urinary retention 39/459 (8.5%) in the renal and urinary disorders SOC.

Other Events of Interest

There were a total of 10 (2.2%) deaths reported in the study. None of the deaths was determined by the investigator to be related to study treatment.

Medical device site erosion was reported by 1 (0.2%) subject in the study. The medical device erosion was determined by cystoscopy. No subjects were observed to have other AEs of interest (e.g., implant tissue necrosis or device dislocation).

Effectiveness Findings

Key effectiveness measures associated with the Stamey Grades indicate that 43% subjects achieved at least a 1-point improvement from baseline to all post-baseline visits (Months 6, 12, 18, 24, 30, and 36). In fact, at the 6 and 12 month visits, approximately 11% of subjects were able to achieve the maximum possible 3-point improvement after COAPTITE® Injectable Implant treatment (subjects with the worst possible Stamey Grade at baseline who achieved a Stamey Grade of 0 (controlled urination); see Table 6).

Table 6 Categorical Summary of Changes in Stamey Grade Over Time – Full Analysis Set (N=458) Baseline Observation Carried Forward

Change in Stamey Grade (Follow-up – baseline)	6 months N (%)	12 Months N (%)
-3	47 (10.3)	48 (10.5)
-2	82 (17.9)	81 (17.7)
-1	100 (21.8)	105 (22.9)
0	192 (41.9)	188 (41.0)
1	29 (6.3)	31 (6.8)
2 (maximum worsening)	8 (1.7)	5 (1.1)
Total number of subjects	458	458

More than 50% of subjects received at least two injections while on study. Ten percent of subjects used alternative treatments for incontinence while 27% required post-treatment only urinary incontinence medications. Mean incontinence quality of life (iQoL) was 40 at baseline and improved to 70-73 for all Months 6, 12, 18, 24, 30, and 36 post-baseline. iQOL is a set of questions that measures the impact of urinary incontinence on quality of life. iQOL is scored from 0-100, and higher scores indicate a better quality of life. Three life quality domains evaluated by iQOL include Social Embarrassment, Psychosocial Impacts, and Activity and Limiting Behavior. An improvement in a mean iQOL of 40 to 70-73 indicates an improvement in quality of life with treatment.

Study Strengths and Weaknesses

This study provides real-world evidence of the safety and effectiveness of COAPTITE® Injectable Implant consisting of a broadly representative patient population and long-term assessment (3 years) in 459 subjects. A weakness of this study is the discontinuation of 116 (25.3%) subjects. Reasons for discontinuation were patient decision, lost to follow-up, death, adverse event, other, and protocol deviation. (see Table 7).

Table 7 Reasons for Discontinuation – Full Analysis Set (N=495) Observed Data

Reason	Number
Lost to Follow-up	35
Adverse Event	6
Death	10
Patient Decision	59
Protocol Deviation	1
Other	5
TOTAL	**116**

While subject discontinuations can bias summaries of study results based on observed data, a broad range of sensitivity analyses were conducted across all effectiveness parameters with no alteration in the underlying conclusions. For example, whereas observed data indicated that between 56-63% of subjects achieved at least a 1-point improvement from baseline to all post-baseline visits in Stamey Grades, if we were to assume that all missing assessments represented situations in which patients returned to their baseline level of disease severity, 43-50% of subjects would still have achieved at least a 1-point improvement from baseline to all post-baseline visits (see Table 8).

Table 8 Sensitivity Analysis: Improvement from Baseline of at least 1 Point in Stamey Grade – Full Analysis Set (N=458)

Visit	6 Month	12 Month	18 Month	24 Month	30 Month	36 Month
	Number of Subjects (n/N) and Percent					
Observed Data	229/408	234/391	208/361	221/350	200/328	199/329
	56.1%	59.8%	57.6%	63.1%	61%	60.5%
BOCF for missing assessment	229/458	234/458	208/458	221/458	200/458	199/458
	50%	51.1%	45.4%	48.3%	43.7%	43.4%

BOCF = baseline observation carried forward

PHYSICIAN TRAINING

To use the COAPTITE® Injectable Implant, physicians must have training in diagnostic and therapeutic cystoscopy.

Patient Counseling

Prior to therapy, the risks and benefits associated with the COAPTITE® Injectable Implant and urethral bulking procedures should be thoroughly discussed with the patient. The 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 the COAPTITE® Injectable Implant 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 Merz North America, 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 typically used for a transurethral injection of the COAPTITE® Injectable Implant:

- 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. The COAPTITE® Injectable Implant 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 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 the COAPTITE® Injectable Implant, 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, the needle must be tightened securely to the syringe. Prime the needle with the COAPTITE® Injectable Implant.** Prepare cystoscopic equipment according to manufacturer's Instructions for Use.

3. The urethra and bladder neck should be examined prior to injection.

WARNING: Following injection of the COAPTITE® Injectable Implant, 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 the COAPTITE® Injectable Implant. (See POST-APPROVAL STUDY section for further information.)
WARNING: Women with peripheral vascular disease and prior pelvic surgery may be at increased risk for tissue erosion following injection of the COAPTITE® Injectable Implant. (See POST-APPROVAL STUDY section 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® Injectable Implant is on the surface of the Luer lock fittings, it will need to be wiped clean with sterile gauze. The syringe 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 the COAPTITE® Injectable Implant 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® Injectable Implant 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 the COAPTITE® Injectable Implant, the needle must be replaced.

6. When the COAPTITE® Injectable Implant 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 ml of the COAPTITE® Injectable Implant, with the average total volume being 4.0 ml. The injection needle already in place may be used with each new syringe or a new injection needle may be used. Regardless, be certain there is no COAPTITE® Injectable Implant 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 the COAPTITE® Injectable Implant 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

The COAPTITE® Injectable Implant is a sterile, non-pyrogenic bulking agent, supplied in single use, latex-free, 1.0 ml syringe. The syringe is packaged in a foil pouch.

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.

WARNING

Contents supplied STERILE using a steam sterilization process. Do not use if sterile barrier is damaged. If damage is found, call your Merz Pharmaceuticals, LLC representative at 1-855-4MERZTX (855-463-7989)
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For single use only. Do not reuse, reprocess, or resterilize. Reuse, reprocessing, or resterilization may compromise the structural integrity of the device and/or lead to device failure which, in turn, may result in patient injury, illness, or death. Reuse, reprocessing, or resterilization may also create a risk of contamination of the device and/or cause patient infection or cross-infection, including, but not limited to, the transmission of infectious disease(s) from one patient to another. Contamination of the device may lead to injury, illness, or death of the patient.

After use, dispose of product and packaging in accordance with hospital, administrative, and/or local government policy.

SHELF LIFE AND STORAGE

The COAPTITE® Injectable Implant 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. Do not use if labeling is incomplete or illegible.

WARRANTY

Merz Pharmaceuticals, LLC warrants that reasonable care has been used 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 express or implied by operation of law or otherwise, including, but not limited to, any implied warranties of merchantability or fitness for a particular purpose.** Handling, storage, cleaning and sterilization of this product as well as other factors relating to the patient, diagnosis, treatment, surgical procedures and other matters beyond Merz Pharmaceuticals, LLC's control directly affect the product and the results obtained from its use. Merz Pharmaceuticals, LLC's obligation under this warranty is limited to the replacement of this product and Merz Pharmaceuticals, LLC shall not be liable for any incidental or consequential loss, damage or expense directly or indirectly arising from the use of this product. Merz Pharmaceuticals, LLC neither assumes, nor authorizes any other person to assume for it, any other or additional liability or responsibility in connection with this product. **Merz Pharmaceuticals, LLC assumes no liability with respect to products reused, reprocessed or resterilized and makes no warranties, express or implied, including but not limited to merchantability or fitness for a particular purpose, with respect to such products.**

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