Carbon Medical Technologies, Inc.

DURASPHERE® *EXP*

Injectable Bulking Agent

DIRECTIONS FOR USE

DESCRIPTION

Durasphere® is a sterile, nonpyrogenic injectable bulking material composed of pyrolytic carbon coated **graphite** beads suspended in a water based carrier gel containing beta glucan. The pyrolytic carbon coated beads are designed to have a minimum dimension of ninety microns and a maximum dimension of two hundred twelve microns.

Durasphere is injected sub-mucosally at the bladder neck. The injection of Durasphere creates increased tissue bulk and subsequent coaptation of the bladder neck and/or urethra. Durasphere should be used only with the Carbon Medical Technologies Injection Needle (specifically CMT catalog numbers 890-XXX).

℞ Only **Caution:** Federal law (U.S.A.) restricts this device to sale, distribution and use by or on the order of a physician trained in diagnostic and therapeutic cystoscopy.

INDICATIONS

Durasphere is indicated for use in the treatment of adult women with stress urinary incontinence (SUI) due to intrinsic sphincteric deficiency (ISD).

CONTRAINDICATIONS

Durasphere must not be used in patients with acute cystitis, urethritis, or other acute genitourinary infection.

The use of Durasphere with needles other than those recommended in this DFU may result in Durasphere beads clogging the injection needle.

WARNINGS

- Do not inject Durasphere into blood vessels. Injection of Durasphere into blood vessels may cause vascular occlusion, platelet aggregation, infarction or embolic phenomena.
- Durasphere should not be used in patients with bladder neck or urethral strictures until such strictures have been corrected. Use of Durasphere on uncorrected strictures may cause occlusion.
- The safety and effectiveness of Durasphere treatment during pregnancy has not been established.
- The effect of Durasphere on subsequent pregnancy and delivery, and the impact of subsequent pregnancy on the effectiveness of Durasphere, is unknown. Therefore, the risks and benefits of the device in women of childbearing potential should be carefully assessed.
- Durasphere containing pyrolytic carbon coated graphite beads is not visible under Xray and requires magnetic resonance imaging (MRI) for visualization.

PRECAUTIONS

- The treatment procedure and instrumentation associated with the injection of Durasphere carry a small risk of infection and/or bleeding, as do similar urologic procedures. The usual precautions associated with urologic procedures, specifically cystoscopy, should be followed.
- Durasphere is supplied steam sterilized in a sealed package and is intended for single use only. Carefully examine the unit to verify that neither the contents nor the sterile package has been damaged in shipment. **DO NOT USE** if damaged. Immediately return damaged product to Carbon Medical Technologies.
- **Do not re-sterilize**. This may damage or distort contents. Unless the packaging is damaged, Durasphere will remain sterile until used or expired.

- Do not expose to organic solvents, ionizing radiation or ultraviolet light. This may damage or distort contents.
- Rotate inventory so that product is used prior to the expiration date on package label.
- After use, treatment syringes and needles may be potential biohazards. Handle accordingly and dispose of in accordance with accepted medical practice and applicable local, state and federal requirements.

ADVERSE EVENTS

The Durasphere clinical trial involved 300 Durasphere treatment injections in 178 patients (mean time in study = 10.7 months, range = 0 to 24.9 months). There were no deaths among the patients injected with Durasphere during the course of this trial.

Observed Adverse Events

Table 1 reports all of the adverse events reported during the clinical study (treatment related and non-treatment related).

Table 1
All Adverse Events (treatment related and non-treatment related)

	# Pts	% Pts	# Events
Urinary tract infection	53	29.8%	64
Urinary urgency	44	24.7%	48
Dysuria	32	18.0%	38
Acute retention (duration ≤ 7 days)	30	16.9%	33
Respiratory (infection)	19	10.7%	21
GI (nausea, vomiting, diarrhea, rectal bleeding, inflammation)	19	10.7%	20
Non-acute retention (duration > 7 days)	19	10.7%	19
Genitourinary (infection, tenderness, urethral prolapse, uterine bleeding, detrusor instability)	17	9.6%	21
Hematuria	12	6.7%	12
Musculoskeletal (back/leg problems, arthritic changes)	10	5.6%	11
Urinary frequency	10	5.6%	10
Outlet obstruction (slow prolonged stream)	8	4.5%	8
Cardiac (angina, MI, hypertension, edema, CAD)	7	3.9%	8
Excreted bulking material	7	3.9%	7
Pain (pelvic, flank, back, ear)	6	3.4%	6
Surgery (hysterectomy, cataract, foot, chole)	6	3.4%	6
Infection (dental, viral, groin)	5	2.8%	6
Accident (fractures/fall)	5	2.8%	5
Overbulking/abscess/cyst	4	2.2%	4
Abnormal lab values	3	1.7%	4
Peripheral vascular (edema, phlebitis)	3	1.7%	3
Dermatology (rash)	3	1.7%	3
Allergic reaction to antibiotic	3	1.7%	3
Fever	3	1.7%	3
Worsening of incontinence (onset of urge)	3	1.7%	3
Neurological (headache, dizziness)	2	1.1%	2
Renal symptom (failure)	1	0.6%	1
Psychological (depression)	1	0.6%	1

A total of 87.6% of all adverse events were classified as *Mild*, 11.6% were classified as *Moderate*, and 0.8% were classified as *Severe*. The three events classified as *Severe* were due to chest pain, renal failure, and myocardial infarction. All three events were reported as unrelated to the device or procedure.

Forty-nine percent (48.6%) of all adverse events were resolved within two weeks of injection, and 91.4% of all adverse events were resolved as of the database cutoff.

Forty-four percent (44.0%) of all the adverse events (included in Table 1) were treatment related. Table 2 displays the treatment related adverse events reported during the clinical study. Treatment related events are those events that the investigator deemed device related or procedure related. Events that were pre-existing, or events that were known by the physician to be unrelated to the device or procedure were classified as non-treatment related. In general, the onset of treatment related events was closer to the treatment date compared to non-treatment related events. For example, the mean number of days between treatment and onset of UTI, urgency, dysuria and non-acute retention was 11 days for treatment related events compared to 126 days for non-treatment related events.

Table 2
Treatment Related Adverse Events

	# Pts	% Pts	# Events
Acute retention (duration ≤ 7 days)	29	16%	32
Dysuria	22	12%	26
Urinary urgency	23	13%	25
Urinary tract infection	16	9%	18
Hematuria	11	6%	11
Non-acute retention (duration > 7 days)	10	6%	10
Outlet obstruction (slow prolonged stream)	8	4%	8
Excreted bulking material	7	4%	7
GI (nausea, vomiting, diarrhea)	7	4%	7
Genitourinary (infection, tenderness)	5	3%	5
Urinary frequency	4	2%	4
Overbulking/abscess/cyst	3	2%	3
Infection	1	< 1%	2
Worsening of incontinence (onset of urge)	1	< 1%	1
Neurological (headache)	1	< 1%	1
Pelvic pain	1	< 1%	1
Allergic reaction to antibiotic	1	< 1%	1
Fever	1	< 1%	1

One hundred-seven patients experienced transient symptoms in the twenty-four hours immediately following injection of Durasphere. Spontaneous resolution of these symptoms by the end of the twenty-four hours is defined as transient. The following transient symptoms were observed during the clinical trial: hematuria (58 patients, 33%), urinary retention (30, 16%), urgency (26, 14%), dysuria (22, 12%), frequency (7, 4%), excreted bulking material (7, 4%), gastrointestinal symptoms (6, 3%), genitourinary symptoms (2, 1%), headache (1, <1%), worsening of incontinence (1, <1%), outlet obstruction (1, <1%), pain (1, < 1%), and fever (1, <1%).

Potential Adverse Events

Based on the literature, possible adverse events that might be expected, but have not been reported as adverse events in the clinical trial include: local tissue infarction and necrosis, embolic phenomena, and vascular occlusion.

CLINICAL STUDIES

PRE-MARKET INVESTIGATION DEVICE EXEMPTION

Purpose of Trial

The purpose of the clinical trial was to evaluate the safety and effectiveness of Durasphere for the treatment of stress urinary incontinence (SUI) due to intrinsic sphincteric deficiency (ISD).

Study Design

The Durasphere clinical study was a prospective, multicenter, double-blind, randomized controlled trial. Patients were randomized (1:1) to either Durasphere containing pyrolytic carbon coated **zirconium** oxide beads (212-500 microns) or a commercially available bulking agent. The transurethral injection procedure was used during the clinical trial for both groups of patients.

The trial had two primary endpoints:

- Improvement in continence grade of patients at 12 months post-treatment compared to baseline.
- Improvement (reduction) in the amount of urine lost by patients who follow a prescribed protocol of activities, at 12 months post-treatment compared to baseline.

Patient continence status was evaluated prior to treatment and at one-, three-, six-, and twelve month follow-up intervals.

Patients Studied

A total of 355 patients were injected with either Durasphere (178 patients) or with the control device (177 patients). All patients were ≥ 21 years of age. The group consisted of patients whose SUI was due to intrinsic sphincter deficiency.

Methods

Continence grades used for the study were as follows:

Grade 0: continent or dry;
Grade 1: patient loses urine with sudden increases in abdominal pressure, but never in bed at night;
Grade 2: patient's incontinence worsens with lesser degrees of stress, such as walking, standing erect from a sitting position, or sitting up in bed;
Grade 3: patient has total incontinence and urine is lost without any relation to physical activity or to position.

Treatment response was determined by grading the patient's incontinence prior to treatment (baseline) and at follow-up. Treatment response was considered to be improved in patients who at any follow-up visit had a decrease in incontinence grade (≥ 1) compared to baseline grade. Treatment response was considered to be dry (Grade = 0) in any patient who after treatment experienced no episode of incontinence between follow-up visits.

Urine loss was quantified through the use of pads that were worn by the patients, and then weighed at the completion of a set of standard activities. The total volume lost during the test period at each follow-up was compared to the volume lost at baseline.

Results

A total of 178 patients were injected with Durasphere. The mean time in the study was 10.7 months.

There were no deaths among the Durasphere patients. There were no reported unanticipated adverse events. Adverse events reported for the Durasphere patient group were similar to those reported for the control group. See Tables 1 and 2 in the Adverse Events section for a listing of the adverse events for the Durasphere patients.

There was no significant difference in the effectiveness of Durasphere compared to the control group; with significantly less injected material required on average to obtain comparable clinical benefit. Tables 3 - 5 summarize the principal effectiveness results of the Durasphere patients. Mean initial volume injected was 4.8 ml for Durasphere and 6.2 ml for the control device ($p < 0.001$).

Table 3
Baseline Information

Number of patients treated	178
Number of patients who had 12 month follow-up	115
Mean age (range)	57.7 years (29 - 84)
Mean duration of incontinence	10.3 years
Mean baseline continence grade score	1.9
Patients with baseline continence grade = 1	19% (34/178)
Patients with baseline continence grade = 2	75% (133/178)
Patients with baseline continence grade = 3	6% (11/178)

Table 4
Treatment Information

Mean number of treatments per patient during study	1.7
Patients receiving a single treatment and followed for 12 months	43% (49/115)
Patients receiving two treatments and followed for 12 months	40% (46/115)
Patients receiving three treatments and followed for 12 months	13% (15/115)
Patients receiving > three treatments and followed for 12 months	4% (5/115)
Mean time between treatments	5.3 months
Mean initial volume injected per patient	4.8 ml
Mean total volume injected per patient	7.6 ml

Table 5
Effectiveness Results

Patients dry (grade = 0) at 12 months	31% (36/115)
Patients improved (≥ 1 grade) at 12 months	66% (76/115)
Patients receiving a single injection and dry (grade = 0) at 12 months	47% (23/49)
Patients receiving a single injection and improved (≥ 1 grade) at 12 months	84% (41/49)
Patients receiving ≥ 2 injections and dry (grade = 0) at 12 months	20% (13/66)
Patients receiving ≥ 2 injections and improved (≥ 1 grade) at 12 months	53% (35/66)
Patients with a baseline grade > 1[+] and dry (grade = 0) at 12 months	31% (29/94)
Patients with a baseline grade > 1[+] and improved (≥ 1 grade) at 12 months	73% (69/94)
Patients dry (grade = 0) at one or more follow-up examination(s)	58% (101/175)
Patients improved (≥ 1 grade) at one or more follow-up examination(s)	90% (158/175)
Mean improvement (decrease) in pad weight at 12 months	27.9 gm (59%)
Mean improvement (decrease) in # incontinence episodes/week at 12 months	20.8 (51%)

[+] Total of 94 patients enrolled with baseline grade > 1 and were followed for 12 months.

POST-APPROVAL STUDY

Carbon Medical Technologies conducted a Post Approval Study to assess the long-term efficacy of Durasphere.

Purpose

The purpose of the Post Approval Study was to collect and analyze long-term efficacy data. This data will be used to predict durability of Durasphere.

Study Design and Population

At the initiation of the Durasphere Post Approval Study, all IDE patients who were improved at twelve months were asked to participate. Once consented to participate, the patient received a self-assessment survey from Carbon Medical Technologies each year for a total of 5 years from the date of their initial treatment. The self-assessment survey is a one-page tool that asks the patients to grade themselves using the same Stamey Score Tool that was utilized in the IDE study.

The patient was also asked to report any additional retreatments with Durasphere or other bulking agents, as well as any other surgical or medical interventions used to improve their urinary incontinence. If the patient reports having other surgical or medical interventions to improve their incontinence, this patient was classified as “efficacy not maintained”.

Duration of the Post Market Study

The progress of each patient in the post market study was followed for a total of five years. The period of five years began with the date of the initial treatment and ended on the fifth anniversary of the initial treatment date.

Primary Endpoint

The primary endpoint is the maintenance in Stamey continence grade score of the patient from baseline at the beginning of the post-approval study to follow up. Maintenance in the continence grade was considered a success for purposes of evaluating this endpoint.

Results

A total of 76 of the original 178 patients (43%) from the IDE study were asked to participate as they were reported as improved at the 12-month follow-up visit in the IDE study. Of these 76, 70 responded by signing a consent to participate in the post-approval study. Of these 70 enrolled, 65 could be located at an average of 5.2 years (range 4.7 – 6.0 years) post initial treatment during the IDE study.

A total of 54.3% (38/70) of the participants enrolled reported their continence grade at this most recent self-assessment to be the same or better than the continence grade they reported at the beginning of the post-approval study. Six of the thirty-eight patients that maintained success (16%) are completely dry. Of the 32 participants categorized as "not maintained", eight received further treatment to improve their stress urinary incontinence. Treatments included surgery, additional bulking procedures and/or medication.

PHYSICIAN TRAINING

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

PATIENT COUNSELING

A Patient Brochure for Durasphere is available by contacting Carbon Medical Technologies at the address on the back cover of this brochure. Use professional judgement to determine if the Patient Brochure is appropriate for patients, relatives, or other interested people.

INDIVIDUALIZATION OF TREATMENT

A complete medical history should be obtained to determine whether the patient is an appropriate candidate for treatment with Durasphere.

Some patients may need additional treatment sessions to achieve and maintain improvement or dryness. If incontinence persists after initial injection or if improvement is followed by recurrence of symptoms, treatment may be repeated after sufficient time has passed to evaluate the patient prior to re-treatment, but in no case should the patient be retreated within 7 days of previous treatment.

Please complete the enclosed Patient Record for each patient treatment and return it to Carbon Medical Technologies.

The patient should be counseled to report adverse events to the treating physician. **Physicians should report device-related adverse events to Carbon Medical Technologies, Inc. at 1-888-207-0262**.

INSTRUCTIONS FOR USE

Injection Procedure

The injection of Durasphere requires Durasphere syringes, Carbon Medical Technologies Injection Needles (CMT catalog numbers 890-XXX), a cystoscope and related accessories.

1. Using standard procedure, prepare the patient for cystoscopy. Insert a cystoscope into the urethra. (For transurethral injection, use a 17 to 24 Fr. cystoscope with a minimum working channel of 5 Fr.)
2. Connect the Durasphere Syringe to the Carbon Medical Technologies Injection Needle (CMT catalog numbers 890-XXX) and prime the needle.

Warning: Do not inject Durasphere into blood vessels. Injection of Durasphere into blood vessels may cause vascular occlusion, platelet aggregation, infarction or embolic phenomena.

Transurethral Injection

3. Advance the needle through the working channel of the cystoscope to the desired injection area.
4. Advance the needle to a point approximately 1 to 1 1/2 centimeters distal to the bladder neck and insert the needle tip under the mucosa. Advance the needle tip one half to one centimeter under the mucosal lining and begin injecting Durasphere. The longitudinal markings are in line with the beveled needle tip. Orient the bevel towards the center of the urethra. A bleb should be visible under direct vision with the cystoscope. If a bleb does not appear, withdraw the needle and reposition more superficially. Inject again.
5. After a bleb has been raised by the injection of Durasphere, reposition the needle away from the initial injection site. Repeat injection procedure until the bladder neck is closed. The procedure typically will require between 4 to 6 ml of Durasphere.

GO TO STEP 6.

Periurethral Injection

3. Introduce the needle approximately 1cm lateral to the urethral meatus.
4. Advance the needle through the perineum, parallel to the urethra, to the desired injection area (submucosal tissue of the proximal urethra). Proceed carefully during the injection procedure to avoid penetration of the urethral lining or bladder. Verify placement of the needle tip cystoscopically by gently moving the needle.
5. Inject Durasphere into the submucosal tissue until unilateral or circumferential closure is seen.
   - If circumferential flow of material is being observed, continue injecting until complete coaptation of the bladder neck is seen with cystoscopic irrigation fluid on. Remove the Injection Needle.
   - If unilateral closure is observed, continue injecting until the submucosal tissue crosses the midline of the urethra. Remove the Injection Needle and repeat on the opposing side. Inject at the second location until coaptation of the bladder neck is seen with cystoscopic irrigation fluid on. Remove the Injection Needle.

6. Since the procedure is dependent on causing the mucosal lining of the bladder neck to balloon up, the treating physician should look for viable mucosal lining.

   NOTE: If the Injection Needle is inserted into muscle rather than submucosal tissue, the Durasphere beads will not flow because muscle is too dense to accept the beads. The Durasphere gel will flow into muscle under extreme force. If this happens, Durasphere beads will clog the Injection Needle.

7. The physician may continue to use the Injection Needle and connect new Durasphere syringes to it or can use a new needle with each syringe of Durasphere.

Caution: After use, treatment syringes and needles may be potential biohazards. Handle accordingly and dispose of in accordance with accepted medical practice and applicable local, state and federal requirements.

It is recommended that patients be kept in the setting or clinic where they receive their Durasphere injection until they are able to void on their own volition. In the event the patient experiences urinary retention, it can be managed by catheterization in the immediate post-injection phase and with clean intermittent catheterization should it persist.

HOW SUPPLIED

Durasphere is provided in individually packaged one (1) ml or three (3) ml syringes. The contents of Durasphere syringes are sterile and nonpyrogenic.

Durasphere is not made with natural rubber latex.

The Durasphere system consists of:

Product	Content	Appropriate Needle(s)
Durasphere 1ml syringe	Approximately 1ml of Durasphere Injectable Bulking Agent	Any CMT catalog number 890-XXX
Durasphere 3ml syringe	Approximately 3ml of Durasphere Injectable Bulking Agent	CMT 1.5in or 3.5in Injection Needle (catalog number 890-XXX)

The items packaged with the Durasphere syringe include the Directions For Use and the Patient Record.

Please call Customer Service toll free at 1-800-258-3476 for ordering information.

STORAGE

There are no special storage instructions for Durasphere (does not require refrigeration). Prior to use, the product should be at room temperature, 15 °C - 32 °C (60 °F - 90 °F).

WARRANTY

The manufacturer warrants that reasonable care has been used in the design and manufacture of this device. 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. Handling and storage of this device as well as factors relating to the patient, diagnosis, treatment, surgical procedures, and other matters beyond the manufacturer's control directly affect the device and the results obtained from its use. The manufacturer's obligation under this warranty is limited to the replacement of this device and the manufacturer shall not be liable for any incidental or consequential loss, damage, or expense directly or indirectly arising from the use of this device. The manufacturer neither assumes, nor authorizes any other person to assume for it, any other or additional liability or responsibility in connection with this device.

Prices and specifications are subject to change without notice.

Durasphere is a registered trademark of Carbon Medical Technologies, Inc.

U.S. Patent Nos. 5,451,406, 5,792,478 and 6,277,392.

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