

Prostatic Artery Embolization Kit

INSTRUCTIONS FOR USE

CAUTION: Federal (U.S.A.) law restricts this device to use by or on the order of a licensed physician

INTENDED USE

The Embosphere PRO Prostatic Artery Embolization Kit, which includes Embosphere[®] Microspheres, is indicated for use in the embolization of prostatic arteries for symptomatic benign prostatic hyperplasia (BPH).

CLINICAL APPLICATIONS FOR BENIGN PROSTATIC HYPERPLASIA (BPH)

Prostatic artery embolization (PAE) is an alternative treatment for men requiring treatment for relief of lower urinary tract symptoms (LUTS) attributable to BPH, such as urinary frequency, inability to urinate, incomplete emptying of bladder, difficulty starting urination, and straining to urinate or urinate in stream.

MAGNETIC RESONANCE IMAGING

Embosphere Microspheres are made of tri-acryl polymer impregnated with porcine gelatin and have no ferrous composition.

DEVICE DESCRIPTION

Embosphere Microspheres are part of a family of embolic materials based on Merit Medical's proprietary microsphere technology. These spheres are designed to offer controlled, targeted embolization.

Embosphere Microspheres are biocompatible, hydrophilic, nonresorbable, microspheres produced from an acrylic polymer and impregnated with porcine gelatin.

DEVICE PACKAGING

- Each Embosphere PRO Prostatic Artery Embolization Kit contains (1) syringe of Embosphere Microspheres (100-300 microns or 300-500 microns), (1) 10 mL syringe, (1) 3 mL syringe, (2) 1 mL syringes, and (1) 3-way stopcock.

- Embosphere Microspheres are contained in a sterile, 20 mL pre-filled syringe, packaged in a peel-away tray.
- Each syringe contains approximately 2.0 mL of Embosphere Microspheres in a pyrogen-free, sterile, physiological saline.
- The kit's syringes and stopcock are sterilized and packaged in a sterile poly pouch.

The following contraindications, warnings, precautions, and instructions for use are applicable to the embolization of prostatic arteries for symptomatic BPH.

CONTRAINDICATIONS

- Patients intolerant to occlusion procedures
- Vascular anatomy or blood flow that precludes catheter placement or embolic agent injection
 - Presence or likely onset of vasospasm
 - Presence or likely onset of hemorrhage
 - Presence of severe atherosclerotic disease
 - Presence of a collateral supply to the lesion not large enough to accept Embosphere Microspheres
- Presence of distal artery vessel pathways potentially endangering normal territories during embolization
- Presence of collateral vessels potentially endangering normal territories during embolization
- Vascular anatomy precluding the free passage of embolic agent through passage of Embosphere Microspheres into the lesion
- In large diameter arteriovenous shunts (i.e., where the blood does not pass through an arterial capillary/venous transition but directly from an artery to a vein)
- In the pulmonary vasculature

PAE Specific Contraindications

- Active urinary tract infection or prostatitis
- Prostate cancer
- Bladder cancer
- Chronic renal failure
- Bladder atonia, neurogenic bladder disorder, or other neurological disorder impacting bladder function
- Bladder stones
- Urinary obstruction due to causes other than BPH, including urethral stricture
- Excessive vesicle tortuosity or severe atherosclerosis

WARNINGS

- Embosphere Microspheres contain gelatin of porcine origin, and therefore could cause an immune reaction in patients who are hypersensitive to collagen or gelatin. Careful consideration should be given prior to using this product in patients who are suspected to be allergic to injections containing gelatin stabilizers.

- Studies have shown that Embosphere Microspheres do not form aggregates, and, as a result, penetrate deeper into the vasculature as compared to similarly sized PVA particles.
- Some of the Embosphere Microspheres may be slightly outside of the range, so the physician should be sure to carefully select the size of Embosphere Microspheres according to the size of the target vessels at the desired level of occlusion in the vasculature and after consideration of the arteriovenous angiographic appearance. The size of Embosphere Microspheres should be selected to prevent passage from artery to vein.

- Serious radiation induced skin injury may occur to the patient due to long periods of fluoroscopic exposure. Large patient diameter, angled x-ray projections, and multiple angled recording runs or radiographs. Refer to your facility's clinical protocol to ensure the proper radiation dose is applied for each specific type of procedure performed. Physicians should monitor patients that may be at risk.

- Onset of radiation-induced injury to the patient may be delayed. Patients should be counseled on potential radiation side effects and whom they should contact if they show symptoms.

- Pay careful attention for signs of mistargeted embolization. During injection carefully monitor patient vital signs to include SaO₂ (e.g., hypoxia, CNS changes). Consider terminating the procedure, investigating for possible shunting, or increasing microsphere size if any signs of mistargeting occur or patient symptoms develop.

- Consider upsizing the microspheres if angiographic evidence of embolization does not quickly appear evident during injection of the microspheres.

PAE Specific Warnings

- A thorough clinical evaluation should be performed on all patients presenting for embolization for BPH (e.g., urinalysis, digital rectal exam, symptom scores, prostate imaging, prostate-specific antigen test, transrectal ultrasound) to rule out prostate cancer.

- Because of the tortuous vessels and duplicative feeding arteries in the pelvic area, extreme caution should be used when performing prostatic artery embolization (PAE). Complications of mistargeted embolization include ischemia of the rectum, bladder, scrotum, penis or other areas.

- When using Embosphere Microspheres for prostatic artery embolization, do not use microspheres smaller than 100 microns. It is recommended to use 300-500 microns.

Warnings About PAE and Fertility

- The effects of PAE on fertility have not been determined. Therefore, this procedure should not be performed on men wanting to father a child.

Warnings About Use of Small Microspheres

- Careful consideration should be given whenever use is contemplated of embolic agents that are smaller in diameter than the resolution capability of your imaging equipment. The presence of arteriovenous anastomoses, branch vessels leading away from the target area or emergent vessels not evident prior to embolization can lead to mistargeted embolization and severe complications.

- Microspheres smaller than 100 microns will generally migrate distal to anastomotic feeders and therefore are more likely to terminate circulation to distal tissue. Greater potential of ischemic injury results from use of smaller sized microspheres and consideration must be given to the consequence of this injury prior to embolization. The potential consequences include swelling, necrosis, fibrosis, abscess and/or stronger post embolization syndrome.

- Post embolization swelling may result in ischemia to tissue adjacent to target area. Care must be taken to avoid ischemia intolerant, nontargeted tissue such as nervous tissue.

PRECAUTIONS

- Patients with known allergy to contrast medium may require corticosteroids prior to embolization.
- Additional evaluations or precautions may be necessary in managing periprocedural care for patients with the following conditions:
 - Bleeding diathesis or hypercoagulable state
 - Immunocompromise

- Do not use if the Embosphere syringe, plunger seal, or tray package appear damaged.
- Do not use if the kit's syringes, stopcock, or pouch appear damaged.

- For single patient use only - contents supplied sterile - never reuse, reprocess, or resterilize the contents of a syringe that has been opened. Reusing, reprocessing or resterilizing may compromise the structural integrity of the device and lead to device failure, which in turn may result in patient injury, illness or death. Reusing, reprocessing or resterilizing 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 diseases) from one patient to another. Contamination of the device may lead to injury, illness or death of the patient. All procedures must be performed according to accepted aseptic technique.

- Do not connect the 20 mL syringe with Embosphere Microspheres directly to a microcatheter for embolic delivery, as a catheter occlusion may result.
- The syringe is intended for embolic use only. Do not use for any other application.

- Embolization with Embosphere Microspheres should only be performed by physicians who have received appropriate interventional embolization training in the region to be treated.

PAE Specific Precautions

- The PAE procedure should only be performed by interventional radiologists who have received appropriate training.
- Collateral circulation may be present and can dilate and supply adjacent arteries as resistance within the prostatic bed increases. Therefore, there is potential for severe complications with nontargeted embolization.

- There is an increased chance of retro-migration of Embosphere Microspheres into unintended blood vessels as prostatic artery flow diminishes. Embolization should be stopped when the vasculature surrounding the prostate can no longer be visualized but before complete stasis in the prostatic artery.

POTENTIAL COMPLICATIONS

Vascular embolization is a high-risk procedure. Complications may occur at any time during or after the procedure, and may include, but are not limited to, the following:

- Paralysis resulting from untargeted embolization or ischemic injury from adjacent tissue edema
- Undesirable reflux or passage of Embosphere Microspheres into normal arteries adjacent to the targeted lesion, through the lesion or into other arteries or arterial beds, such as the internal carotid artery, pulmonary, or coronary circulations
- Pulmonary embolism due to arterial venous shunting
- Ischemia at an undesirable location, including ischemic stroke, ischemic infarction (including myocardial infarction), and tissue necrosis
- Capillary bed occlusion and tissue damage
- Vessel or lesion rupture and hemorrhage
- Vasospasm
- Recanalization
- Foreign body reactions necessitating medical intervention
- Infection necessitating medical intervention

- Complications related to catheterization (e.g., hematoma at the site of entry, clot formation at the tip of the catheter and subsequent dislodgment, and nerve and/or circulatory injuries, which may result in leg injury)
- Allergic reaction to medications (e.g., analgesics)

- Allergic reaction to contrast media or embolic material
- Pain and/or rash, possibly delayed from the time of embolization
- Death
- Blindness, hearing loss, loss of smell, and/or paralysis

- Additional information is found in the Warnings section

PAE Specific Potential Complications

- Nontargeted embolization of the rectum, bladder, scrotum, penis, or other areas
- The most frequent post-procedure complication includes "Post-PAE Syndrome", which includes nausea, vomiting, fever, pelvic pain, burning sensation, dysuria, and frequent or urgent urination
- Skin burn (radiation exposure) from prolonged fluoroscopy time
- Blood in urine, semen, or stool
- Bladder spasm
- Hematoma at the catheter site
- Urinary tract infection
- Urinary retention
- Constipation

STORAGE AND STERILITY

- Embosphere Microspheres must be stored in a cool, dry and dark place in their original syringe and packaging.
- Use the Embosphere Microspheres by the date indicated on the syringe label.
- Do not freeze the Embosphere Microspheres.
- Do not resterilize the Embosphere Microspheres.
- Use the kit's syringes and 3-way stopcock by the date indicated on the pouch.
- Do not resterilize the syringes and 3-way stopcock.

INSTRUCTIONS FOR USE

Inspect packaging prior to use to ensure seal integrity for maintenance of sterility.

- Carefully evaluate the vascular network associated with the lesion using high resolution imaging prior to beginning the embolization procedure.

- The Embosphere PRO Prostatic Artery Embolization Kit contains Embosphere Microspheres in 100-300 microns or 300-500 microns size ranges. Because of the potential for misembolization and the inherent variability in sphere sizes, the physician should be sure to carefully select the size of Embosphere Microspheres according to the size of the target vessels at the desired level of occlusion in the vasculature.

- For prostatic artery embolization, it is recommended to use Embosphere Microspheres 300-500 microns.

- Choose a delivery catheter based on the size of the target vessel and the microsphere size being used. Embosphere Microspheres can tolerate temporary compression of up to 33% to facilitate passage through the delivery catheter.

- Introduce the delivery catheter into the target vessel according to standard techniques. Position the catheter tip as close as possible to the treatment site to avoid inadvertent occlusion of normal vessels.

- Embosphere Microspheres are not radiopaque. It is recommended that the embolization be monitored using fluoroscopic visualization by adding the appropriate amount of contrast medium to the physiologic suspension fluid.

To Deliver Embosphere Microspheres

- Match the total volume in the syringe with the same volume of undiluted contrast, which will result in a 50% microsphere/saline and 50% contrast solution. Remove all air from the syringe. To evenly suspend the Embosphere Microsphere/contrast solution, gently invert the 20 mL syringe several times. Attach the 20 mL syringe to one port of the 3-way stopcock. Attach a 1 mL or 3 mL injection syringe to another port on the stopcock and, if desired, a delivery catheter may be attached to the remaining port on the stopcock. Wait several minutes to allow the Embosphere Microspheres to suspend in the solution. Draw the Embosphere Microspheres/contrast solution into the injection syringe slowly and gently to minimize the potential of introducing air into the system. Purge all air from the system prior to injection. Inject the Embosphere Microspheres/contrast solution under fluoroscopic visualization with the injection syringe using a slow pulsatile injection while observing the contrast flow rate. If there is no effect on the flow rate, repeat the delivery process with additional injections of the Embosphere Microspheres/contrast solution. If the Embosphere Microspheres/contrast solution requires re-suspension, gently invert the 20 mL syringe several times. Exercise conservative judgment in determining the embolization endpoint.

- Femoral puncture can result in arterial spasm. This may predispose to femoral thrombosis (e.g., leg injury). Femoral puncture should be re-assessed prior to final catheter removal.
- Upon completion of the treatment, remove the catheter while maintaining gentle suction so as not to dislodge Embosphere Microspheres still within the catheter lumen.
- Apply pressure to the puncture site until hemostasis is complete.
- Discard any open, unused Embosphere Microspheres.

Additional PAE Specific Instructions

- A Foley catheter, with its balloon inflated with a mixture of contrast and saline, may be placed prior to PAE for use as a landmark during the embolization procedure.
- PAE can be performed by either radial or femoral access.

PATIENT COUNSELING INFORMATION

- Patients should have a clear understanding prior to embolization of who will provide their post procedure care and whom to contact in case of an emergency after embolization.
- Embolization patients should have an understanding of the potential benefits, risks, and adverse events associated with embolization. In particular, patients should understand that there is a chance their symptoms will not improve following embolization.

PAE CLINICAL SUMMARY

A Composite database from clinical trials and published literature containing information from a total of 286 patients who underwent prostatic artery embolization (PAE) using Embosphere Microspheres for treatment of symptomatic benign prostatic hyperplasia (BPH) was analyzed to evaluate clinical outcomes. All patients were suffering from lower urinary tract symptoms (LUTS) due to BPH, with International Prostate Symptom Scores (IPSS) of moderate to severe. Prostate or bladder cancer; active urinary tract infections or prostatitis; bladder stones; and antia or other neurogenic conditions impacting bladder function, and intolerance to contrast media or catheter-based interventions were exclusionary. Prior to embolization, patients underwent clinical evaluation, imaging of the prostate, and completed validated symptom and quality of life questionnaires. Follow-up evaluations included the IPSS and its quality of life (QOL) questionnaire and prostate imaging at a minimum. The primary effectiveness evaluations were change in IPSS and QOL scores post embolization, with reduction in prostate size as a secondary objective. Safety was assessed from reported adverse events.

RESULTS

Mean age of the evaluated cohort was in the seventh decade, lower urinary tract symptoms were severe as reflected in a mean IPSS score over 20, and quality of life was dissatisfied to unhappy. Fifty-four patients had indwelling bladder catheters at baseline.

Table 1 – Baseline Characteristics of the Patient Population

Characteristic	Mean ± SD	n
Age (years)	67.7 ± 9.7	286
IPSS	21.5 ± 6.8	251
Quality of life	4.6 ± 0.9	166
Prostate volume (gms)	85.1 ± 38.3	265
PSA (ng/mL)	5.4 ± 4.6	251
Omax (mL/s)	6.9 ± 3.8	175

The majority of patients underwent bilateral embolization.

Table 2 – Unilateral versus Bilateral Embolization

Embolization	Patients (%)
Unilateral	29 (10.1)
Bilateral	254 (88.9)
No data	3 (1.0)

Mean symptom scores, which were severe at baseline, improved compared to pretreatment values in every follow-up interval. Values at the 9- to 16-month evaluation period were mildly symptomatic. A reduction of IPSS by at least 3 points was achieved at this latest evaluation in 97% of patients, and 90% followed by at least 1 symptom category.

Table 3 – Mean IPSS at Baseline and Follow-up

Time Window	Mean ± SD	n
Baseline	21.5 ± 6.8	251
1 to 3 months f/u	6.3 ± 5.8	190
9 to 16 months f/u	6.2 ± 5.8	136

Table 4 – Proportion of Patients Achieving ≥ 3-point Improvement in IPSS

Time Window	Proportion (95% CI)
1 to 3 months f/u	0.889 (0.872-0.909)
9 to 16 months f/u	0.897 (0.831-0.943)

Table 5 – Proportion of Patients Achieving ≥ 1 IPSS Category Improvement

Time Point	Proportion (95% CI)
1 to 3 months f/u	0.842 (0.782-0.891)
9 to 16 months f/u	0.897 (0.831-0.943)

Not surprisingly, the reduction of lower urinary tract symptoms reflected in the IPSS changes affected mean quality of life. Mean QOL scores, which were categorized as mostly dissatisfied to unhappy pre-embolization, improved at every follow-up interval to pleased/mostly satisfied.

Table 6 – Mean Quality of Life at Baseline and Follow-up

Time Point	Mean ± SD	n
Baseline	4.8 ± 0.9	166
1 to 3 months f/u	1.4 ± 1.2	116
9 to 16 months f/u	1.4 ± 1.1	165

Mean prostate size at baseline was 85.1 g, and demonstrated reduction throughout follow-up.

Table 7 – Mean Prostate Volume at Baseline and Follow-up

Time Point	Mean ± SD	n
Baseline	85.1 ± 38.3	265
1 to 3 months f/u	62.4 ± 27.1	193
9 to 16 months f/u	65.2 ± 28.6	118

In addition to the overall composite population, analyses were done for subsets of patients age 80 or older, with prostate 90g or larger, and those with indwelling catheters at baseline for management of acute urinary retention. These categories are not mutually exclusive. Patients in these groups were of particular interest because they frequently are re-catheterized for TURP; prostate size larger than 90g are typically referred for open surgery, and patients in acute retention are not generally treated by transurethral procedures. For these reasons the successful outcomes from PAE in these cohorts is notable.

Other than being older, baseline evaluations of the ≥80-year subset were similar to those of the Composite group, including IPSS reflecting severe symptoms and mostly dissatisfied to unhappy quality of life.

Table 8 – Baseline Characteristics of Patients Age ≥ 80 Years

Characteristic	Mean ± SD	n
Age (years)	84.6 ± 3.8	39
IPSS	23.9 ± 9.9	32
Quality of life	4.6 ± 1.2	17
Prostate volume (gms)	78.1 ± 27.0	34
PSA (ng/mL)	3.9 ± 3.6	22

* 13 of 39 patients (33.3%) had indwelling bladder catheters at baseline

Although elderly patients might be limited in treatment options and/or might be more fragile due to comorbidities, this cohort achieved reduction in LUTS at all follow-up intervals. Over 80% had at least a 3-point reduction in IPSS and a substantial majority dropped by at least one symptom category.

Table 9 – Mean IPSS at Baseline and Follow-up of Patients Age ≥ 80 Years

Time Window	Mean ± SD	n
Baseline	23.9 ± 9.9	32
1 to 3 months f/u	13.4 ± 9.2	9
9 to 16 months f/u	7.0 ± 2.9	9

Table 10 – Proportion of Patients Age ≥ 80 Years Achieving ≥ 3 Point IPSS Improvement

Time Window	Proportion (95% CI)
1 to 3 months f/u	0.889 (0.518-0.997)
9 to 16 months f/u	0.889 (0.831-0.977)

Table 11 – Proportion of Patients Age ≥ 80 Years Achieving ≥ 1 IPSS Category Improvement

Time Point	Proportion (95% CI)
1 to 3 months f/u	0.778 (0.404-0.972)
9 to 16 months f/u	0.667 (0.300-0.925)

The mean quality of life for this group trended toward improvement from mostly dissatisfied to mostly satisfied.

Table 12 – Mean Quality of Life at Baseline and Follow-up of Patients Age ≥ 80 Years

Time Window	Mean ± SD	n
Baseline	4.6 ± 1.2	17
1 to 3 months f/u	1.4 ± 0.9	8
9 to 16 months f/u	1.1 ± 1.1	10

Bilateral embolization was possible in 80% of this group, and prostate size reduction was seen throughout follow-up.

Table 13 – Unilateral versus Bilateral Embolization in Patients Age ≥ 80 Years

Embolization	Patients (%)
Unilateral	4 (20.0)
Bilateral	31 (75.0)
No data	0 (0.0)

Table 14 – Mean Prostate Volume at Baseline and Follow-up of Patients Age ≥ 80 Years

Time Point	Mean ± SD	n
Baseline	78.1 ± 27.1	34
1 to 3 months f/u	55.1 ± 27.5	16
9 to 16 months f/u	64.6 ± 20.6	10

Among the subset of patients with prostate size larger than 90g, baseline characteristics were similar to those of the entire Composite group, other than gland volume.

Table 15 – Baseline Characteristics of Patients with Prostate Size ≥ 90g

Characteristic	Mean ± SD	n
Age (years)	68.4 ± 9.0	195
IPSS	19.8 ± 6.8	87
Quality of life	4.6 ± 0.8	53
Prostate volume (gms)	124.2 ± 35.5	95
PSA (ng/mL)	7.4 ± 5.5	88

* 12 of 95 patients (12.6%) had indwelling bladder catheters at baseline

Symptoms improved in this cohort post embolization at all time points, and a minimum 3-point reduction and drop of at least one symptom category in IPSS was achieved by 96% and 89% of patients respectively.

Table 16 – Mean IPSS at Baseline and Follow-up of Patients with Prostate Size ≥ 90g

Time Window	Mean ± SD	n
Baseline	19.8 ± 6.8	87
1 to 3 months f/u	5.0 ± 4.6	69
9 to 16 months f/u	4.6 ± 4.1	54