

Instructions for Use Microsulis Microwave Endometrial Ablation (MEA) System

CAUTION: FEDERAL LAW (USA) RESTRICTS THIS DEVICE TO SALE BY OR ON THE ORDER OF A PHYSICIAN TRAINED IN DIAGNOSTIC HYSTEROSCOPY AND IN THE USE OF THE DEVICE.

READ ALL INSTRUCTIONS, CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS PRIOR TO USE. FAILURE TO FOLLOW ANY INSTRUCTIONS OR TO HEED ANY CONTRAINDICATIONS, WARNINGS OR PRECAUTIONS COULD RESULT IN SERIOUS PATIENT INJURY.

TO REPORT ADVERSE EVENTS (INCLUDING PATIENT INJURY AND DEVICE MALFUNCTIONS), PLEASE CALL MICROSULIS (1-800-830-4904). (Federal law requires the reporting of instances in which a device may have caused or contributed to a death or serious injury.)

This document provides instructions for using the MEA System including the treatment Applicator. Please refer to the Operator's Manual for set-up and complete instructions.

PHYSICIAN CHECKLIST

The physician must:

- Be skilled in diagnostic hysteroscopy and have adequate training, knowledge, and familiarity with the MEA System.
- Review and be familiar with these Instructions for Use and the Operator's Manual
- Complete the MEA training program conducted by Microsulis-certified clinical personnel or Microsulis-approved physician trainers. This includes performing a minimum of three (3) treatments under their guidance.
- Be aware of the need to abort the procedure in the event that
 - The hysteroscopic examination does not confirm the integrity of the uterine cavity.
 - The MEA Applicator insertion length differs by (i.e. is greater than or less than) more than 5mm from the pre-operative uterine sound measurement, or
 - The system detects an abnormal initial temperature rise upon activation of the microwave energy source, which may indicate incorrect Applicator placement and a possible uterine wall perforation.
- Ensure that pre-MEA ultrasound (to determine minimum myometrial thickness) and post-dilation hysteroscopy (to confirm that no uterine wall trauma occurred during dilation) have been performed prior to MEA treatment as described in the Instructions for Use and in the Physician Training material.
- Never remove the MEA Applicator before first taking his/her foot off of the pneumatic footswitch.

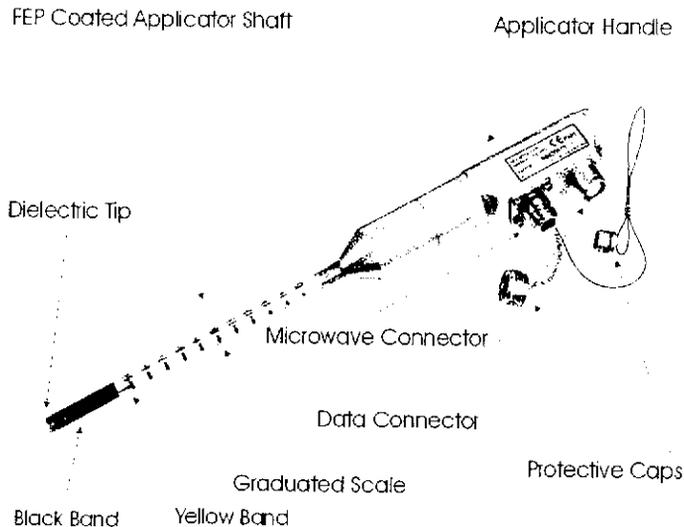
SUPPORT PERSONNEL

Adjunct support personnel should be familiar with the Operator's Manual, training video and other training materials prior to operating the MEA System.

DEVICE DESCRIPTION - MEA SYSTEM and REUSEABLE APPLICATOR

The Microwave Endometrial Ablation (MEA) System is a device designed to ablate the endometrial lining of the uterus using microwave energy at a fixed frequency. It consists of the MEA System Control Unit that houses a Control Module with an embedded microprocessor and a

touch screen user interface with color display, a microwave generator, and a power supply. Additional components include a hand-held reusable Applicator, a pneumatic footswitch, microwave and data transmission cables, a printer (optional), a power cord, and a portable cart.



The MEA Applicator serves as the interface between the Microwave generator and the patient. It is a one-piece reusable instrument used to introduce microwaves at 9.2 GHz into the uterus via the cervix. The Applicator is primarily an aluminum assembly comprised of a main body and the shaft (or waveguide) for a total length of 338mm. The shaft measures 8.5 mm in diameter and is approximately 18 cm in length. It is graduated along its length in centimeter units. A solid black band located 35 mm below the tip is used to indicate to the physician the tip position with respect to the endocervical canal. A solid yellow band located adjacent to the black band is used to call attention to the imminent appearance of the black band during treatment. The ceramic tip is 7.0 mm in length.

The Applicator is connected to the MEA Control Unit by two cables. The microwave cable carries the energy from the microwave generator to the MEA Applicator. The data cable has two functions: (i) to carry temperature data from the MEA Applicator, allowing for continuous temperature monitoring of the tissue in the treatment field; and (ii) to communicate with a "smart chip" located in the main body of the MEA Applicator to monitor usage.

The MEA Applicator is inserted into the uterine cavity until the Applicator tip reaches the fundus. The microwave energy is applied by depressing the footswitch connected to the MEA Control Unit. Microwave energy emanates hemi-spherically from the MEA Applicator tip and is absorbed by the surrounding endometrial tissue. The display screen is viewed continuously during the treatment to monitor the temperature at the tip of the Applicator. The MEA Applicator is moved slowly from side to side in the fundal area until the temperature reaches 70°C. Once the fundal area is completely treated, the side-to-side movements are continued while simultaneously withdrawing the MEA Applicator from the uterine cavity. The MEA system achieves endometrial ablation by heating a 5-6 mm layer of tissue (endometrium plus myometrium) to therapeutic temperature levels. The duration of the treatment is generally between three and five minutes for the normal sized uterus (sounding length 75-85 mm). When the black band on the MEA Applicator is visible at the external cervical os, the footswitch is released, which deactivates the microwave energy and the MEA Applicator is fully withdrawn.

INDICATIONS

The MEA System is intended to ablate the endometrial lining of the uterus in pre-menopausal women with menorrhagia (excessive uterine bleeding) due to benign causes for whom childbearing is complete.

37

CONTRAINDICATIONS

The MEA treatment is contraindicated for use in women:

- who have a myometrial thickness of less than 10mm in any area of the uterus, as determined by transvaginal ultrasound of the entire corpus.
- who have uterine perforation or wall damage observed or suspected during pre-procedure hysteroscopy.
- **in whom the MEA Applicator has been re-inserted following prior treatment or partial treatment.**
- who have undergone any previous endometrial ablation procedure.
- who are pregnant or who desire to become pregnant in the future.
Pregnancies following ablation can be dangerous for both mother and fetus.
- with known or suspected endometrial carcinoma (uterine cancer) or pre-malignant conditions of the endometrium, such as unresolved (atypical) adenomatous hyperplasia.
- with mechanical endometrial thinning for pre-treatment, such as dilation and curettage (D&C), or suction aspiration, as thinning of the uterine wall may result.
- with any anatomic or pathologic condition in which weakness of the myometrium could exist, such as classical cesarean section or transmural myomectomy.
- with active genital or urinary tract infection at the time of the procedure (e.g., cervicitis, vaginitis, endometritis, salpingitis, or cystitis).
- with an intrauterine device (IUD) currently in place.
- with a uterine sounding length of less than 6 cm.
- with active pelvic inflammatory disease.
- with undiagnosed vaginal bleeding.
- with Essure contraceptive micro-inserts.

WARNINGS

SONOGRAPHIC EVALUATION OF MYOMETRIAL THICKNESS

- IN ALL CASES, transvaginal ultrasound must be performed prior to MEA treatment to confirm that the myometrial portion of the uterine wall is greater than or equal to 10mm throughout the uterus, including in the uterine cornua and the lower uterine segment. (Serious injury to tissues adjacent to the uterus has occurred following MEA in patients with a thin uterine wall.) See "Ultrasound Evaluation of the Myometrium Prior to MEA Treatment" section of this document.
- It is recommended that a second transvaginal ultrasound be performed within 10 days prior to MEA in order to evaluate the effects of the GnRH analog if such an agent is used for endometrial preparation in the following patients:
 - patients who have a myometrial wall measurement between 10-12 mm, as determined by the initial screening ultrasound, and
 - patients who have a history of low transverse Cesarean section or other surgical procedure or condition that could place her at increased risk of myometrial thinning
 - patients who have received more than one 30-day dose of GnRH therapy

HYSTEROSCOPIC EVALUATION OF THE ENDOMETRIAL CAVITY

- IN ALL CASES, hysteroscopy must be performed following cervical dilation and prior to insertion of the MEA Applicator to ensure that neither perforation nor uterine wall damage has occurred. (Serious injury to tissues adjacent to the uterus has occurred following MEA in patients with unrecognized wall damage with and without perforation.)
- Following hysteroscopy to confirm uterine wall integrity, it is essential that the uterine cavity be drained of fluid prior to commencing the MEA procedure. The irrigation channel/channels should be opened and left to drain at the conclusion of hysteroscopy to ensure the uterine cavity has been emptied of irrigation fluid. Failure to remove fluid may result in an incorrect environment for the use of MEA. Fluid inside the uterine cavity may interfere with proper microwave induced heating of the endometrium (and potentially reduce treatment efficacy) because the fluid can absorb the microwave energy emitted from the Applicator.

UTERINE PERFORATION/DAMAGED UTERINE WALL

- Use caution so as not to perforate the uterine wall when sounding the uterine cavity, dilating the cervix, and inserting the MEA applicator.
 - (The risks associated with damaging the uterine cavity when dilating, may be reduced by ensuring that the dilator's passage does not extend too far beyond the internal cervical os into the uterine cavity.)
- Cavity Length Discrepancy: The MEA procedure **must be aborted** if the MEA Applicator insertion length differs by (i.e. is greater than or less than) more than 5mm from the pre-operative uterine sound measurement.
- The MEA System performs a temperature profile evaluation (Temperature Rise Gate-TRG) at the **start** of each procedure to confirm performance of the MEA Applicator and to detect abnormal temperature rises that may indicate incorrect Applicator placement and a possible uterine wall perforation.

If the TRG activates, the procedure must be aborted to prevent the possibility of damage to adjacent organs.
- A thorough evaluation of the patient should be conducted prior to discharge of patients for whom perforation was confirmed or suspected.

GENERAL

- Endometrial ablation using the MEA Thermal Ablation System is not a female sterilization procedure. Therefore, the patient should be advised of appropriate birth control methods.
- Endometrial ablation is intended for use only in women who do not desire to bear children because the likelihood of pregnancy is significantly decreased following the procedure. Pregnancy following ablation may be dangerous for both the mother and the fetus.
- Endometrial ablation does not eliminate the potential for hyperplasia or adenocarcinoma of the endometrium and may mask the physician's ability to detect or make a diagnosis of such pathology.
- Patients who undergo endometrial ablation procedures who have previously undergone tubal ligation are at increased risk of developing post ablation tubal sterilization syndrome which can require hysterectomy. This can occur as late as 10 years post procedure.

TECHNICAL

- Adhere to the Microsulis Training and Instructions for Use regarding the correct use of MEA Applicator. Do not attempt to achieve temperatures greater than the therapeutic temperature range of 70° – 80° C by moving the Applicator too slowly. Prolonged exposure to temperature levels above this range may increase the risk of thermal injury to tissue in contact with the uterine serosa.
- Prior to use all applicators must be fully sterilized in accordance with the instructions given in Section 3.4 of the MEA Operator's Manual. Do not proceed with applicators that have not been sterilized.
- RF Radiation – exposure of the human body to microwave radiation can constitute a hazard (NRPB Consultative Document Dec. 1982/ANSI C95-1). Personnel must be protected from microwave energy produced by the magnetron oscillator. All RF connectors must be correctly fitted before operation so that no leakage of RF energy can occur. The microwave power source must not be operated unless the output connection is correctly terminated. It is particularly hazardous to look into open waveguides, coaxial feeders or transmitter antenna when the device is operating.
- Never attempt to simulate body temperature to override interlocks in order to allow the applicator to function. Never hold the applicator in your hand to see if the tip gets warm. This will coagulate tissue in your hand and result in a deep (3-6mm) burn.

PRECAUTIONS

- Patients with a severely anteverted, retroverted, or laterally displaced uterus are at greater risk of uterine wall perforation during any intrauterine manipulation or instrumentation. Caution should be taken during the dilation process to avoid creation of a false passage or perforation using the cervical dilator.
- Patients with serosal adhesions involving adjacent organs, especially bowel, may be at greater risk of serious complication following MEA.
- A false passage can occur during any procedure in which the uterus is instrumented, especially in cases of severe anteverted, retroverted, or laterally displaced uteri. Use caution to ensure that the device is properly positioned within the uterine cavity.
- Patients who have undergone endometrial ablation and are later placed on hormone replacement therapy should have a progestin included in their medication regimen in order to avoid the increased risk of endometrial hyperplasia or adenocarcinoma associated with unopposed estrogen replacement therapy.
- Patients should have had a normal pap smear within one year, and an endometrial biopsy to confirm benign endometrium within 6 months prior to undergoing MEA.
- The safety and effectiveness of the MEA treatment has not been fully evaluated in patients:
 - with a uterine sounding length of 12 cm or greater
 - with bicornuate septate, or septate uteri
 - with transabdominal metallic tubal occlusion devices
 - who are post-menopausal
 - with submucosal fibroids that distort the endometrium more than 3cm or that obstruct access to the uterine cavity
 - with medical pre-treatment options other than GnRH agonists (ie. OCP, progestogens, or cycle timing)
 - with connective tissue disorders
- The MEA System consists of the following components:
 - MEA Control Unit
 - MEA Applicator
 - MEA Microwave Cable

- MEA Data Transmission Cable
- MEA Foot Switch
- MEA Power Cord

To ensure proper operation, never use other components with the MEA system.

- Do not attempt to repair the MEA Applicator, MEA cables or MEA Control Unit. If problems are suspected, call Microsulis Customer Service for instructions.
- The user should inspect the MEA Applicator and cables for damage prior to use.
- Cables should be positioned such that contact with patient or other leads (cables) is avoided.
- To protect the MEA Applicator Connectors from liquids, do not immerse in water, clean or sterilize the MEA Applicator without first securing the connector caps.
- Applicators should always be cleaned and then disinfected or sterilized immediately after an MEA procedure or if any form of contamination is suspected.
- The plastic sheath on the Applicator, while durable in normal use, is susceptible to damage from knocks against sharp objects. If damage to the Applicator is observed or suspected, or if moisture is visible under the sheath or the sheath has moved, then the Applicator must not be reused and the incident must be reported to Microsulis.
- Ensure the connector caps are replaced securely after use and before the Applicator is immersed in liquid or exposed to steam. If the covers become damaged, detached or missing, do not continue to sterilize or reuse the Applicator. Contact Microsulis.
- **Continued operation of the MEA when the black band is visible could result in thermal injury to the endocervical canal.**
- Failure to follow the correct shutdown procedure may lead to loss of data and faulty system operation.
- The MEA Applicator is a sophisticated but delicate piece of equipment and must be treated with appropriate care to ensure its continued effectiveness and longevity.
- When handling an applicator prior to a procedure, all necessary precautions to ensure the sterile integrity of the applicator must be taken. Handling of the applicator must only be undertaken by personnel who are fully qualified to undertake the handling of sterile equipment.
- The system is powered from high voltage and must be properly grounded.
- The system produces microwave energy which can damage body tissue if the system is not used correctly.
- Recommended procedures must be followed when handling sterilized equipment.
- The printer must not be connected to any power source other than the supply socket on the rear of the control unit. This is to ensure that the printer is isolated from the main supply in the event of a printer fault condition. (The system provides printer power via an isolating transformer for safety in the event of a printer fault.)
- The MEA system must not be used with the rear cover removed. This cover must only be removed by authorized personnel.
- The MEA Applicator must not be connected to any other source of microwave power or instrumentation.
- Medical protective gloves must be worn at all times when handling used or contaminated applicators.
- High voltage – hazardous voltages are present within the microwave power source when it is operating normally. The unit has been designed to prevent personnel coming into contact with hazardous voltages, and must not be used with the cover removed. There are no user serviceable parts within the unit. **If the unit is malfunctioning, faulty or damaged it must be returned to Microsulis for repair. All maintenance must be carried out by Microsulis.**
- Earthing – the microwave power source is designed to be connected to earth via the m5 stud located on its rear panel. This must not be removed.
- Recommended procedures must be followed when handling contaminated equipment

41

- The printer must not be connected to any power source other than the supply socket on the rear of the MEA unit. This is to ensure that the printer is isolated from the mains supply in the event of a printer fault condition.

ADVERSE EVENTS

The MEA System was evaluated in a randomized, prospective, multi-center clinical trial of 324 patients with abnormal uterine bleeding comparing the MEA System to a control arm of hysteroscopic rollerball endometrial ablation (REA). Tables 1 through 4 summarize the adverse events reported during the first one-year follow-up for all patients entered in this study. Some patients had more than one event in a given time period.

Table 1 Intra-Operative Adverse Events

	MEA N (% of 216)	REA N (% of 108)
Cervical laceration	2 (0.9%)	2 (1.9%)
Cervical stenosis	1 (0.5%)	0 (0.0%)
Pre-treatment uterine perforation*	2 (0.9%)	0 (0.0%)
*Both perforations occurred with a cervical dilator during dilation. Patients did not receive ablation treatment.		

Table 2 Post-Operative Adverse Events – Within 24 Hours

	MEA N (% of 216)	REA N (% of 108)	p-Value
Chills	19 (8.8%)	7 (6.5%)	0.523
Dysuria	17 (7.9%)	11 (10.2%)	0.531
Fever	2 (0.9%)	0 (0.00%)	0.554
Headache	6 (2.8%)	4 (3.7%)	0.736
Nausea	49 (22.6%)	18 (16.6%)	0.245
Vomiting	29 (13.4%)	4 (3.7%)	0.006
Urinary tract infection	1 (0.5%)	1 (0.9%)	1.000
Uterine cramping*	155 (71.8%)	64 (59.3%)	0.032
Abdominal tenderness	11 (5.1%)	9 (8.3%)	0.327
Bloating	15 (6.9%)	9 (8.3%)	0.657
* The use of pre-operative and post-operative pain medication was not standardized within the study protocol. As such, the use of pain medication was left to the discretion of the physician and patient.			

42

Table 3 Post-Operative Adverse Events – Within 24 Hours to Two Weeks

	MEA N (% of 216)	REA N (% of 108)	p-Value
Chills	3 (1.4%)	0 (0.0%)	0.553
Dyspareunia	1 (0.5%)	0 (0.0%)	1.000
Endometritis	6 (2.8%)	0 (0.0%)	0.184
Fever	3 (1.4%)	1 (0.9%)	1.000
Headache	8 (3.7%)	4 (3.7%)	1.000
Nausea/Vomiting	3 (1.4%)	1 (0.9%)	1.000
Urinary tract infection	1 (0.5%)	0 (0.0%)	1.000
Bacteremia	1 (0.5%)	0 (0.0%)	1.000
Uterine cramping	11 (5.1%)	7 (6.5%)	0.613
Abdominal tenderness	7 (3.2%)	4 (3.7%)	1.000
Vaginal discharge/infection	5 (2.3%)	0 (0.0%)	0.174

Table 4 Post-Operative Adverse Events – Within Two Weeks to 1 Year

	MEA N (% of 216)	REA N (% of 108)	p-Value
Dysuria	1 (0.5%)	1 (0.9%)	1.000
Dyspareunia	2 (0.9%)	0 (0.0%)	0.554
Dysmenorrhea	8 (3.7%)	3 (2.8%)	0.757
Endometritis	2 (0.9%)	1 (0.9%)	1.000
Headache	7 (3.2%)	3 (2.8%)	1.000
Nausea/Vomiting	3 (1.4%)	0 (0.0%)	0.553
Post-ablation pregnancy	0 (0.0%)	1 (0.9%)	1.000
Urinary tract infection	6 (2.8%)	4 (3.7%)	0.736
Uterine cramping	19 (8.8%)	3 (2.8%)	0.059
Vaginal discharge/infection	20 (9.3%)	11 (10.2%)	0.842

This table reports individual events documented at the 3,6, and 12 months post-procedure reporting periods. Multiple events may have occurred in the same patient.

Note: Transmyometrial thermal damage and thermal injury to adjacent organs in the absence of uterine perforation can occur in cases where the integrity of the uterine wall is either damaged, partially perforated, or thinned. Patient injury associated with this hazard has occurred during commercial use of the MEA system outside of the United States (14 reported cases in over 15,000 procedures). At the time of these injuries, ultrasound evaluation of the uterine wall was not utilized and the use of hysteroscopy prior to treatment with the MEA System was optional. The use of ultrasound to measure uterine wall thickness during the screening of all patients and the use of hysteroscopy to confirm an intact uterine cavity prior to treatment with MEA were safety measures used in the pivotal clinical trial of MEA.

ANTICIPATED POST-PROCEDURAL COMPLICATIONS

For any endometrial ablation procedure, commonly reported post-operative events include the following:

- Cramping/pelvic pain. Post-treatment cramping can range from mild to severe. This cramping will typically last a few hours but may continue beyond the first day following the procedure
- Nausea and vomiting (possibly attributable to certain types of anesthesia) have been reported in patients immediately following the procedure and can be managed with medication.
- Vaginal discharge
- Vaginal bleeding/spotting

OTHER ADVERSE EVENTS

As with all endometrial ablation procedures, serious injury or death can occur. The following adverse events could occur or have been reported in association with the use of the MEA System:

- Thermal injury to adjacent tissue
- Hematometra
- Hemorrhage
- Uterine perforation
- Post-ablation tubal sterilization syndrome
- Pregnancy and/or complications of pregnancy (Pregnancies following endometrial ablation can be dangerous for both mother and fetus.)
- Risks associated with hysteroscopy
- Infection or sepsis
- Complications leading to serious injury or death

PRE-OPERATIVE MEA PROCEDURES

The use of ultrasound and hysteroscopy as pre-operative procedures is necessary for the safe use of the MEA system. Important information on the hysteroscopic examination and the ultrasound evaluation is provided in the sections below.

HYSTEROSCOPIC INVESTIGATIONS

A hysteroscopic examination of the uterine cavity must be performed after cervical dilation, prior to the insertion of the MEA Applicator.

- A hysteroscopic examination of the uterine cavity is undertaken to confirm integrity of the uterine cavity. Hysteroscopy is intended to allow the physician to detect uterine wall damage, perforation, false passage, focal indentations or thinning, all of which could potentially lead to patient injury. A satisfactory hysteroscopic procedure is one in which there is adequate cavity distention, where clear visualization of both tubal ostia is achieved, and where the evaluation of an intact endometrium is possible. The inability to clearly visualize normal uterine cavity landmarks is an indication to avoid performance of the MEA treatment. **Serious injury to tissue adjacent to the uterus has occurred following MEA in patients with unrecognized uterine wall damage.**

In all cases the hysteroscopic investigation is used to confirm an intact, undamaged uterine cavity. This process will ensure that the MEA treatment is not performed in the presence of a false passage or uterine wall perforation.

The MEA procedure must be abandoned if a damaged uterine cavity is identified or suspected during hysteroscopic examination.

Hysteroscopy should be performed in accordance with the labeling and instructions for use as provided by the manufacturer of the hysteroscope being employed.

ULTRASOUND EVALUATION OF THE MYOMETRIUM PRIOR TO MEA TREATMENT

OBJECTIVE

Evaluation of the myometrium and endometrium by ultrasound is generally included as part of the prudent evaluation of abnormal uterine bleeding. Such evaluation is required for appropriate evaluation of the patient being considered for MEA treatment. The primary goals of ultrasound evaluation are to ensure (1) there are no areas of the myometrial wall less than 10 mm in thickness, and (2) there are no fibroids that obstruct access to the uterine cavity. It is recommended that physicians be familiar with "Guidelines for Performance of the Ultrasound Examination of the Female Pelvis" published by the American Institute for Ultrasound in Medicine and with the American College of Obstetrician and Gynecologists standard for performance of saline infusion sonohysterography.

In general, transvaginal ultrasound is the preferable method for evaluating the uterus for the purposes of determining the minimal myometrial thickness. In some cases, alternative methods may be necessary. If there is poor visualization on transvaginal ultrasound, you should perform saline infusion sonohysterography. In addition, if the uterine cavity is ≥ 14 centimeters in length transabdominal ultrasound may be necessary.

EQUIPMENT

Ultrasound dynamic examination of the pelvis should be conducted using standard suitably cleaned and protected vaginal 5MHz or greater frequency transducers with appropriate gain, image size and depth settings for optimal image acquisition. A lower frequency abdominal transducer is needed for adequate examination of large uteri or for guidance of insertion of a cervical dilator, uterine sound or the MEA Applicator itself into the uterine cavity, if necessary.

Diagnostic quality images for documentation of pathology and of standard midsagittal and transverse uterine images, as well as of the actual myometrial thickness should be made using video tape, film, paper printer, or a retrievable digital format. Saline infusion sonohysterography, if deemed necessary, should be performed with a sterile syringe of saline and a sterile 2 or 3mm catheter. The imager must be experienced in gynecologic/vaginal ultrasound.

TIMING OF EVALUATION

When MEA treatment is a consideration, ultrasound examination of the uterus is a required component of patient screening. The ultrasound evaluation should take place shortly prior to the recommended GnRH analog pre-treatment (3.75 mg im of leuprolide acetate depot administered 3-5 weeks prior to MEA). This screening ultrasound should be scheduled within the first week of menses or a progestin withdrawal bleed. The functionalis endometrial layer is shed by the fourth day of bleeding, leaving only a 1mm basalis layer unless there is endometrial pathology. The double-layer endometrial thickness should measure no more than 5mm after shedding and should not be included in the myometrial measurements. Saline infusion sonohysterography is

recommended for definition and measurement of the myometrial contours if the endometrium is poorly defined.

Special attention should be paid to the specific evaluation of the myometrial thickness as described below.

When MEA treatment is under consideration, the regularity and thickness of the myometrium is of great importance. GnRH analogues reduce uterine size, therefore myometrial thickness, by suppressing estrogen. Therefore, short-term suppression of myometrium is best assessed by a second vaginal ultrasound not more than 10 days before the MEA in the following patients:

- For patients whose initial screening ultrasound revealed myometrial thickness between 10 to 12 millimeters. The purpose of this second ultrasound is to be certain that the myometrial thickness has not diminished below 10 millimeters as a result of GnRH therapy. If the second ultrasound procedure determines that the myometrium is less than 10 millimeters, treatment with the MEA System will not proceed.
- For patients with uterine scars, including those from low transverse cesarean section or other uterine surgical procedure or condition that could place her at increased risk of myometrial thinning following GnRH;
- For any patient who has received more than one 30-day dose of GnRH therapy

GUIDANCE FOR ULTRASOUND EXAMINATION OF THE UTERUS

In all patients the entire uterine wall must be scanned systematically using vaginal ultrasound (VU). If the endometrium is not clear, saline infusion sonohysterography will delineate the cavity and cesarean section scars. Calibrated three dimensional imaging is convenient, accurate and fast, but not always available. Special attention should be paid to the lower uterine segment in patients with a history of low transverse cesarean section. In these patients, measurement of the lower uterine segment should be made within 1cm of the internal cervical os. Special attention should also be paid to specific regions of the uterine wall involved by prior surgical manipulation (e.g., myomectomy or resection of septum).

1. With the subject in modified dorsal lithotomy position, with her head and torso elevated at least 30 degrees above the horizontal plane, insert the sheathed vaginal transducer in the sagittal orientation into the vagina, watching as the cervix is approached.

2. CERVIX: The primary landmark. Image the entire length of the cervical canal in order to determine the orientation of the uterus. Locate the internal os and use the cervical canal to orient to the midsagittal plane of the uterus.

3. SAGITTAL MANEUVER: Fan across from cornu to cornu to survey the symmetry and thickness of the endometrium and myometrium, then return to the midsagittal plane to measure from basalis to serosa at the thinnest point of each wall and the mid fundus.

4. UTERINE LENGTH: Internal os to fundal serosa in the sagittal view. Axial or midposition uteri should be manipulated so that the angle of insonation is perpendicular to the long axis of the uterus.

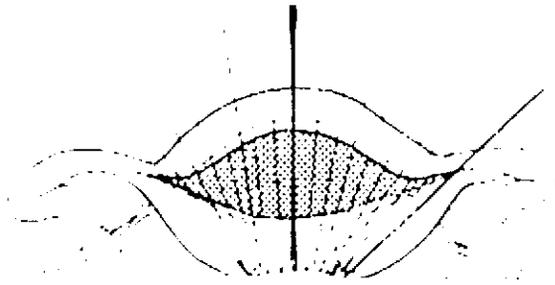
5. AP DIAMETER of each wall at the fundus: Anterior serosa to endometrium; posterior serosa to edge of posterior endometrium. Low transverse cesarean section scars are best delineated when they contain fluid, and may be subtle otherwise.

6. **UTERINE WIDTH** at the fundus from serosa to serosa; include the uterine/ cornual vessels. After the Sagittal Maneuver, turn the transducer a quarter turn to image the transverse plane of the uterus, keeping the uterus in the middle of the screen and as well oriented as possible. **Transverse Maneuver:** Scan from the cervix to the fundus, maintaining contact with the uterus through the vaginal wall. **MYOMETRIAL THICKNESS:** Measure each lateral wall from the lateral basalis endometrium to the lateral uterine serosal surface at the narrowest point of the myometrium, which is often at the cornua.

Summary of Maneuvers and Examples of Measurements:

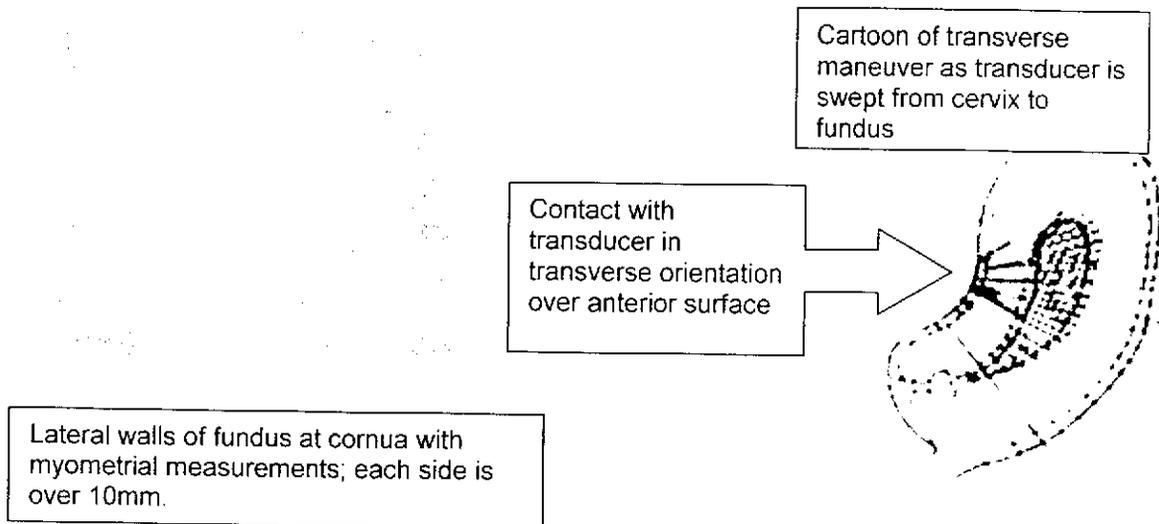


Mid-sagittal uterine image with myometrial measurements (yellow lines) at thinnest region of myometrium, from the edge of the basalis layer of endometrium to the fundal serosa. There is an anterior fundal myoma. Myometrial measurements do not include the endometrium.



Cartoon of the Sagittal Maneuver as the transducer is swept across the uterus to create a mental 3D image of the fundus

Contact with sagittally oriented transducer over anterior surface of anteverted uterus



DOCUMENTATION OF THE SCAN

A report of the ultrasound findings must be included as part of each patient's medical record. Specific recording of the uterine wall thickness and any abnormalities should be documented on the Microsulis Patient Assessment Form. A record of the ultrasound examination should be retained in accordance with requirements of the applicable regulations of the State Medical Board in which the examination was performed.

Reference

1. American Institute of Ultrasound in Medicine, *Guidelines for Performance of the Ultrasound Examination of the Female Pelvis*, 1995.
2. American College of Obstetrics and Gynecology, *Saline Infusion Sonohysterography*, 2003.

CLINICAL STUDY

Purpose: The use of the MEA System in the treatment of excessive uterine bleeding from benign causes in pre-menopausal women was compared to Rollerball Endometrial Ablation (REA) to evaluate safety and effectiveness.

Study Endpoints: The primary effectiveness measure was a validated menstrual diary scoring system developed by Janssen (Janssen CAH, Scholten P, Heintz PM. A simple visual assessment technique to discriminate between menorrhagia and normal menstrual blood loss. *Obstet Gynecol*, 1995;85:977-982). Patient success was defined as a reduction in diary score from ≥ 185 pre-treatment to ≤ 75 at 1 year post-treatment. Study success was defined as a statistical difference of less than 15% in patient success rates between MEA and REA. Secondary endpoints included anesthesia regimen, anesthesia time, duration of procedure, responses from a quality of life questionnaire, and amenorrhea rate. Safety evaluation was based on the adverse events reported during the study, including device-related complications.

Study Methodology: A randomized (2:1) prospective study was conducted at clinical sites and included 324 patients diagnosed with excessive menstrual bleeding. Menstrual diary scores were collected pre-treatment and monthly for 12 months post-treatment. All patients were given a

single hormonal pre-treatment of leuprolide acetate depot (3.75 mg i.m) to thin the endometrial lining and received ablation treatment within 3-5 weeks after administration. Study subjects were required to meet the following inclusion/exclusion criteria:

Inclusion criteria

- Patient had excessive bleeding with a documented PBLAC score greater than or equal to 185, previously had failed medical therapy (eg. oral contraceptives or progestins), and would have been offered endometrial ablative surgery or hysterectomy as a treatment for menorrhagia
- Patients with previous diagnosis had failed, was unable to tolerate, or refused medical therapy (required 1 month (1 cycle) documentation)
- Patients presented to the study without documented failed medical treatment (required 3 month (3 cycle) documentation, with a PBLAC average of > 185)
- Patient was over 30 years of age and pre-menopausal at enrollment as determined by FSH measurement less than or equal to 30 I.U./mL⁽¹²⁾
- Patient was an appropriate candidate for general or local anesthesia
- Patient was not pregnant and had no desire to conceive at any time
- Patient agreed not to use hormonal contraception or any other intervention for bleeding during the study
- Patient had benign endometrium on preoperative endometrial sampling
- Uterine sounding was less than or equal to 14cm

Special Precautions

- Connective tissue disorder(s) and long term steroid therapy
 - Increased caution in sounding, dilation and fundal treatment due to status of tissue acutely retroverted and/or fixed uteri
 - Increased caution in sounding and dilation
- Bicornuate uteri
 - The use of abdominal ultrasound is used to insure correct placement of the Applicator in each horn and to ensure that both horns are treated

Exclusion Criteria

- Menopausal women (as indicated by elevated FSH level >30 I.U./mL)
- Presence of submucosal fibroids that obstructed treatment access to any part of the endometrial cavity (as determined by hysteroscopy)
- Uterus sounded <6 cm
- Previous endometrial ablative surgery

- Previous classical cesarean section
- Any portion of uterine wall measured <8 mm in thickness as determined by pelvic ultrasound in both the transverse and sagittal views, measuring the distance between the uterine cavity and uterine serosa (uterine wall thickness)
- Presence of IUD
- Women who were pregnant or still desired to conceive.
- Presence of atypical endometrial hyperplasia, (i.e. adenomatous) or endometrial carcinoma on preoperative endometrial sampling
- Presence of active endometritis
- History of gynecological malignancy within past 5 years
- Active Pelvic Inflammatory Disease (PID)
- Known clotting defects or bleeding disorders
- Untreated/unevaluated cervical dysplasia

Patient Population: The mean patient age was 40.5 ± 4.6 years (MEA) and 40.9 ± 4.6 years (REA) with a proportionate distribution of patients both under 40 years of age and over 40 years of age for both groups. There were no statistical differences between the two treatment groups with regard to age, race, body mass index, mean diary scores or uterine cavity length or among the eight investigational sites. The table below describes the accountability of subjects throughout the study period:

Table 5 Patient Accountability

	MEA N	REA N	Totals N
Patients Enrolled	216	108	324
Patients Enrolled but Not Treated			
Cavity access limited	3	1	4
Cervical stenosis	1	0	1
Pre-treatment uterine perforations	2	0	2
Patients Treated	210	107	317
Patients for whom 12 month data not available			
Lost to follow-up	11	6	17
Patient withdrew participation after treatment*	2	4	6
Deceased (automobile accident)	1	0	1
Subject completed 12 month visit, started HRT month 9 (PBLAC invalid)	1	0	1
Subject completed 12 month visit, PBLAC lost	1	1	2
Patients Evaluated Post-Op 12 Months (YTD)	194	96	290

*Includes 2 patients treated at McGill University which withdrew site participation. These two patients were excluded from the intent-to-treat group for the Effectiveness: Bleeding Rates evaluation.

50

Effectiveness

Effectiveness: Bleeding Rates

Patient success was based on a reduction in diary score from ≥ 185 to ≤ 75 at one year post-treatment. Table 6 shows the success rates for 322 patients in the intent-to-treat group. (Two patients are not included in this analysis due to one sites discontinuation from the study as indicated in the Patient Accountability table.)

Table 6 Effectiveness: Bleeding Rates– Intent-to-Treat Group

	MEA n=215	REA n=107	p-Value
Successful patients ⁽¹⁾	187	89	
Success rate (95% Confidence Interval)	87.0% (81.7-91.2%)	83.2% (74.7-89.7%)	0.399⁽²⁾
Amenorrhea patients ⁽³⁾	119	49	
Amenorrhea rate (95% Confidence Interval)	55.3% (48.4-62.1%)	45.8% (36.1-55.7%)	0.124⁽²⁾
This table presents Intent-to-Treat success rates. Seven patients (6 MEA and 1 REA) were not treated on the operative day. 13 MEA patients and 9 REA (control) patients were lost to follow up. Three additional subjects (2 MEA & 1 REA) did complete the 12 month visit; however a diary score was not available. These patients were considered failures in calculating success rates.			
⁽¹⁾ Success is defined as a diary score of ≤ 75 .			
⁽²⁾ P-value obtained from Fisher's Exact Test. The p-value from the protocol specified primary efficacy analysis employing Blackwelder's Z statistic with an acceptable difference of $\leq 15\%$ is <0.001 indicating that the MEA success rate is not inferior to that of REA.			
⁽³⁾ Amenorrhea is defined as a diary score of zero (0).			

The effectiveness of MEA in treating menorrhagia patients who also had small cavity distorting fibroids (≤ 3 cm distortion of endometrial stripe on transvaginal ultrasound) was compared against REA. As can be seen in the table below, the efficacy of either the MEA or REA procedure in women with fibroids was lower than treatment in women without fibroids.

Table 7 Effectiveness: Bleeding Rates (Fibroid Analysis) – Intent-to-Treat Group

	MEA n=215	REA n=107
Patients with fibroids	41	30
Successful patients	28	23
Success rate fibroids	68.3%	76.7%
Patients without fibroids	174	77
Successful patients	159	66
Success rate no fibroids	91.4%	85.7%

Effectiveness: Quality of Life

Patient satisfaction was assessed by administering Quality of Life (Short Form-36) questionnaires prior to treatment and at 3, 6, and 12 months post-treatment. Significant reductions in patient-reported dysmenorrhea and increases in quality of life scores were experienced by both groups. Overall treatment satisfaction and acceptance of the operation were similar for both groups. Table 7 shows the patient responses at 12-months post-treatment. Percentages are calculated based on the number of responders (Evaluable Group).

51

Table 8 Effectiveness: Quality of Life Data at One Year–Evaluable Group

	MEA n (%)	REA n (%)	p- Value
Number of patients responding	196	97	
Acceptance of operation			
Positive	194 (99.0%)	97 (100.0%)	1.000
Negative	2 (1.0%)	0 (0%)	
Overall treatment satisfaction			
Very satisfied / Satisfied	193 (98.5%)	96 (99.0%)	1.000
Dissatisfied	3 (1.5%)	1 (1.0%)	
Dysmenorrhea			
Pre-treatment	176 (89.8%)	86 (88.7%)	1.000
Post-treatment	66 (33.6%)	33 (34.0%)	1.000
Evaluable patient population does not include those patients not treated or lost to follow-up. The three subjects (2 MEA & 1 REA) who completed the 12 month visit, but for whom a diary score was unavailable, are included in the quality of life analysis.			

Safety

Procedure Time

Procedure time was determined by recording the time of device activation. Mean procedure time for the MEA group was significantly less than the mean time for the REA group as shown in Table 8 below.

Table 9 Procedure Time

	MEA n=209	REA n=106	p-Value
Mean (minutes)	3.45	20.26	<0.0001
Std. Deviation (minutes)	1.02	15.60	

Anesthesia Regimen and Anesthesia Time

The clinical protocol did not specify the type of anesthesia to be used in either treatment group. The decision of which type of anesthesia to use was governed by physician discretion and patient preference. The type and total time of anesthesia that was administered to each patient was recorded. Additional anesthesia-use analysis is presented after removing one study site that used general anesthesia exclusively for all MEA and REA patients. Exclusive use of general anesthesia was due to concomitant research activities within one of the investigational sites, in which patients agreed to undergo MEA treatment under local anesthesia. Only those patients with a preference to have general anesthesia were offered to participate in this trial. The tables below show the number of patients receiving which type of anesthesia and the mean anesthesia time for both treatment groups. The mean anesthesia time for the MEA treatment group was significantly less than the mean anesthesia time for the REA group.

52

Table 10 Anesthesia Use – Controlled at One Site

Anesthesia Type	MEA n=209	REA N=106
General	44.5% (93/209)	78.3% (83/106)
IV Sedation	54.1% (113/209)	16.0% (17/106)
Regional	0.5% (1/209)	3.8% (4/106)
IV Sedation plus regional	1.0% (2/209)	1.9% (2/106)

Table 11 Anesthesia Use – Patient and Physician Choice

Anesthesia Type	MEA n=183	REA N=95
General	36.6% (67/183)	75.8% (72/95)
IV Sedation	61.7% (113/183)	17.9% (17/95)
Regional	0.5% (1/183)	4.2% (4/95)
IV Sedation plus regional	1.1% (2/183)	2.1% (2/95)

*Patients receiving treatment at Aberdeen Royal Infirmary were treated using general anesthesia only and are excluded from this analysis.

Table 12 Anesthesia Time

	MEA n=209	REA n=106	p-Value
Mean (minutes)	39.26	47.10	0.007
Std. Deviation (minutes)	25.44	23.40	

Clinical Study Observations

Hysterectomy

Two patients (1 MEA and 1 REA) had a hysterectomy within one year post treatment. The REA patient presented at the 6-month follow-up visit with a PBLAC score of 20, a success by menstrual bleeding score. At seven months post-treatment she had a hysterectomy due to dissatisfaction attributed to menstrual bleeding. The MEA patient presented within three months post treatment with severe left-sided pelvic pain, which was complicated by a left adnexal mass. She underwent a total abdominal hysterectomy with bilateral salpingo-oophorectomy with benign findings.

53

PATIENT SELECTION

Menorrhagia can be caused by a variety of underlying conditions, including but not limited to, endometrial cancer, leiomyomata, polyps, medications, infection, and dysfunctional uterine bleeding (anovulatory bleeding). Patients should always be evaluated appropriately to determine the cause of excessive uterine bleeding before any treatment is initiated.

Consult medical literature relative to various endometrial ablation techniques, indications, contraindications, complications, and hazards prior to the performance of any endometrial ablation procedure.

PATIENT COUNSELING

As with any procedure, the physician should discuss risks, benefits, and alternatives with the patient prior to performing endometrial ablation. The patient should understand that the aim of the treatment is the reduction in bleeding to normal levels.

The MEA procedure is not a sterilization procedure. Subsequent pregnancies may be dangerous for the mother and fetus. The MEA Thermal Ablation System is intended for use only in women who desire no further childbearing because the likelihood of pregnancy is significantly decreased following the procedure. Patients of childbearing capacity should be cautioned of potential complications, if they were to become pregnant. This counseling should include the need for post-procedure contraceptive use where indicated.

Vaginal discharge is typically experienced during the first few weeks following endometrial ablation and may last for as long as a month. Generally, the discharge is described as bloody during the first few days; then may be profuse and watery thereafter. Any unusual or foul-smelling discharge should be reported to the physician immediately. Other common post-procedural complications include cramping/pelvic pain, nausea, and vomiting.

Uterine perforation should be considered a possibility in the differential diagnosis of post-operative complaints, including but not limited to, acute abdominal pain, fever, shortness of breath, dizziness, and hypotension. Patients should be counseled that any such symptoms should be reported to their physician immediately.

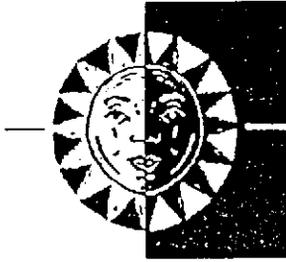
Patients who undergo the recommended pre-MEA hormonal endometrial thinning should be counseled that it is possible that the uterine wall may be too thin at the time of MEA treatment to qualify for MEA.

PRE-TREATMENT PREPARATION OF PATIENT

It is recommended that patients undergoing MEA be pre-treated with a GnRH analog as was done for subjects in the pivotal clinical trial of the MEA. (In the pivotal trial, all patients were given a single hormonal pre-treatment of leuprolide acetate depot (3.75 mg i.m) to thin the endometrial lining and received ablation treatment within 3-5 weeks after administration.)

It is also recommended that a nonsteroidal anti-inflammatory medication (NSAID) be administered at least one hour prior to treatment and continued postoperatively as needed to reduce intraoperative and postoperative uterine cramping.

54



MICROSULIS AMERICAS

1(800) 830-4904
Email: info@microsulis.com
www.microsulis.com

Microsulis Americas December 2002