SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. GENERAL INFORMATION

DEVICE GENERIC NAME:	Thermal (Microwave Frequency) Endometrial Ablation Device
DEVICE TRADE NAME:	Microwave Endometrial Ablation (MEA) System
APPLICANT'S NAME AND ADDRESS:	Microsulis Medical Limited Parklands Business Park Denmead Hampshire PO7 6XP England
U.S. REPRESENTATIVE:	Microsulis Corporation 7508 Alafia Drive Riverview, FL 33569
PREMARKET APPROVAL APPLICATION (PMA) NUMBER:	P020031
DATE OF PANEL RECOMMENDATION:	June 10, 2003
DATE OF NOTICE OF APPROVAL TO THE APPLICANT:	September 23, 2003

II. INDICATIONS FOR USE

The **Microwave Endometrial Ablation (MEA) System** is a thermal ablation device 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.

III. CONTRAINDICATIONS

Use of the Microwave Endometrial Ablation System (hereafter referred to as MEA System) 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.

IV. WARNINGS AND PRECAUTIONS

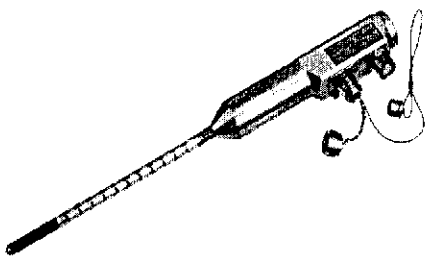
A listing of Warnings and Precautions can be found in the device labeling.

V. DEVICE DESCRIPTION

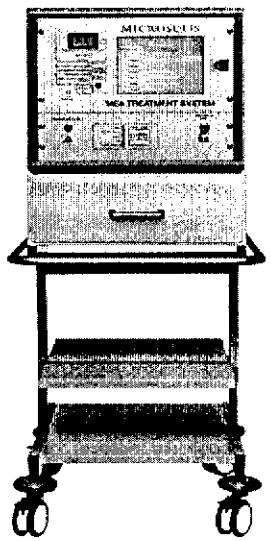
The Microwave Endometrial Ablation System (MEA) is a software-controlled device designed to ablate the endometrial lining of the uterus using microwave energy at a fixed frequency. The MEA System consists of the following parts:

- MEA Applicator
- MEA Console (includes control unit, microwave generator, and power module)
- MEA Microwave Cable
- MEA Data Transmission Cable
- MEA Foot Switch
- MEA Power Cord
- A sterile camera/laser drape sheath is an off-the-shelf component

Pictorial representations of the MEA Console and reusable Applicator are shown below:



MEA Applicator



MEA Console

Reusable Applicator

The Applicator serves as the interface between the Microwave Module 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 338 mm in length and is primarily an aluminum assembly comprising a main body, and the applicator shaft (or waveguide). The shaft measures 8.5 mm in diameter and is graduated along its length in whole centimeter units. A solid black band extending 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 extending 7 mm beyond the black band is used to call attention to the imminence of the black band during treatment. The ceramic tip is 7.0 mm in length.

The applicator includes two thermocouples. One thermocouple measures the tip temperature and the other measures the temperature along the shaft.

The applicator is connected to the MEA system by two cables. The coaxial cable carries the microwave energy from the microwave module to the applicator. The data cable has two functions: (1) to carry temperature data from the MEA

Applicator, allowing for continuous temperature monitoring of tissue in the treatment field; and (2) to communicate with a "smart chip" located in the main body of the MEA Applicator to monitor the number of Applicator uses. The "smart chip" is set to allow 30 uses of one Applicator.

The Applicator is supplied non-sterile and is designed to be cleaned and steam sterilized by the user prior to use. The entire operative end of the MEA Applicator is encapsulated with Fluorinated Ethylene Propylene (FEP). It should not be disassembled or tampered with in any way or connected to any other microwave equipment.

MEA Console

The console contains the control unit, microwave generator and power module. The control module contains the hardware and software components necessary to guide the user with system and treatment instructions for safe operation of the MEA System. The MEA System is operated via a resistive touch panel (touch screen) installed in the control module. Using the touch screen, the operator can control all aspects of its operation.

In addition to providing the user touch screen, the front panel of the console contains the start button and emergency stop button. The front panel also provides information on the Applicator tip and treatment temperature indicators, system status, power output and power-reflected.

The microwave frequency chosen for the MEA System is 9.2 GHz. The operating power is 42 watts. This frequency and power are associated with a deposition of microwave energy 3.3 mm into the uterine tissue. Although the microwave energy is only deposited 3.3 mm, thermal conduction carries the heat generated deeper into the uterine tissue.

Principle of Operation

With the MEA Applicator positioned in the endometrial cavity, microwave energy is emitted from the ceramic tip of the Applicator. The microwave energy heats the endometrium, causing the temperature to rise. The Applicator includes a temperature sensor embedded in its tip. A Data Cable connected to the Applicator transmits temperature measurements obtained from the sensor to a color display providing the physician with real-time visual feedback of the treatment temperature. This temperature response at the beginning of each treatment does not vary significantly from patient to patient and as a result, a software "gate" was designed to analyze the temperature rise to detect abnormal rise times. If this rise is abnormal the power is inhibited and the treatment is discontinued. If the rise is normal the procedure can begin. The target temperature range is 70-80 °C. Once this temperature is reached, the Applicator can be moved. When the Applicator tip is moved to an untreated area, the temperature falls. The physician uses this

graphical response to control the depth and coverage of heating during the MEA treatment. The system achieves endometrial ablation by heating a 5-6 mm layer of intrauterine tissue to therapeutic temperature levels for the duration of the treatment, which averages 3 ½ minutes for the normal size uterus (75-85 mm).

Treatment Technique

Once the physician determines that a patient is an appropriate candidate for the ablation procedure with MEA (by performing a screening evaluation including transvaginal ultrasound to confirm that the myometrium is at least 10 mm thick throughout the uterus), the patient should be given a dose of medication (e.g., 3.75 mg Depo Lupron i.m.) to thin the lining of the uterus approximately three to five weeks prior to the procedure. If the patient's initial screening ultrasound revealed a myometrial thickness between 10 and 12 mm or if the patient has a uterine scar or has received more than one 30-day dose of GnRH therapy, a second transvaginal ultrasound should be performed to assess the myometrial thickness within 10 days of the MEA treatment. On the day of the procedure, the patient is administered the appropriate anesthesia. After uterine sounding and dilation, the uterine cavity must be examined using hysteroscopy to verify that the cavity is intact. The 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 control unit. The physician monitors the temperature at the tip by continuously viewing the display on the console. An area is considered treated once the temperature has reached the therapeutic band, i.e., 70 – 80 °C. Once the fundal area is completely treated, the treatment is continued with side-to-side movements while simultaneously withdrawing the Applicator from the uterine cavity. When the Applicator tip reaches the internal cervical os, the footswitch is released, which deactivates the microwave energy and the Applicator is fully withdrawn.

VI. ALTERNATIVE PRACTICES OR PROCEDURES

The following alternative practices and procedures are currently available to treat excessive uterine bleeding due to benign causes:

Drug Therapy

Drug therapy, using estrogen-progestogen combinations (such as those found in oral contraceptives) or progestogens (progesterone) by themselves, is frequently employed for the treatment of menorrhagia. Other classes of drugs used include androgens such as danocrine, gonadotropin-releasing hormone (GnRH) analog, and non-steroidal anti-inflammatory drugs (NSAIDs). Drug therapy is typically the first order treatment to alleviate excessive menstrual bleeding. Drug therapies usually require long term treatment. They are successful for some patients, but for

others they are ineffective and may introduce unpleasant side effects. Drug therapy does, however, allow the woman to maintain her fertility.

Dilatation and Curettage (D&C)

D&C is typically the first surgical step if drug therapy is unsuccessful in eliminating excessive bleeding. First the cervix is dilated, then the uterine contents are either scraped away by an instrument or removed through vacuum aspiration. This may reduce bleeding for a few cycles. If a polyp is present and removed, the bleeding may stop. In most cases, it does not provide the patient with long-term definitive results. It is useful, however, for those women who desire to maintain their fertility.

Hysteroscopic Endometrial Ablation

Hysteroscopic endometrial ablation is a surgical procedure which utilizes a resectoscope or operating hysteroscope, a video monitor, a fluid distention medium such as glycine or sorbitol, and a surgical ablation device such as an electrode loop, rollerball or laser to destroy the inner lining of the uterus, the endometrium. The procedure is typically performed under general or epidural anesthesia. The cervix must be dilated to accommodate the hysteroscopic instrument, and the uterus must be properly distended. The most common risks associated with hysteroscopic endometrial ablation are hyponatremia from fluid overload, which is a life-threatening condition, and uterine perforation. This treatment is intended for women who no longer desire to maintain their fertility.

Thermal Endometrial Ablation

Thermal endometrial ablation is a surgical procedure in which the endometrium is treated with heat for a pre-determined period of time. This treatment can be performed by utilizing a variety of methods to heat the endometrial lining, including the use of hot fluids injected directly into the uterine cavity or into a balloon-like device in the uterine cavity. The procedure may be performed under general or local anesthesia with intravenous sedation. Dilation of the cervix to 5-8 mm may be required. This treatment is intended for women who no longer desire to maintain their fertility.

Cryosurgical Ablation

In cryosurgical ablation, a surgical device is used to destroy tissues of the uterus using extreme cold. A probe is inserted into the uterus under ultrasound guidance for pre-determined periods of time, and the tip of the probe is cooled to temperature of -100° to -120°C. The procedure may be performed under general or local anesthesia with intravenous sedation. Dilation of the cervix to 6-7 mm may be required. This treatment is intended for women who no longer desire to maintain their fertility.

Non-hysteroscopic Radiofrequency Ablation

In non-hysteroscopic radiofrequency (RF) ablation, a surgical device is used to destroy tissues of the uterus using electrical energy delivered via a conformable bipolar electrode array. This array is introduced through the cervix in a slender tube. Once in the uterus it expands into a triangular mesh. Electrical energy is then delivered to the mesh which causes vaporization and/or coagulation of the endometrium. The procedure may be performed under general or local anesthesia with intravenous sedation. Dilation of the cervix to 8 mm may be required. This treatment is intended for women who no longer desire to maintain their fertility.

Hysterectomy

Historically, the most common and definitive surgical treatment for menorrhagia is hysterectomy. It is, however, a major surgical procedure performed in the hospital under general anesthesia and is associated with the risks and complications of major surgery. Depending on the technique, it may require a lengthy recovery period.

VII. MARKETING HISTORY

The MEA System has been commercially marketed internationally since 1996. At the time of approval, the Microwave Endometrial Ablation System was available in Australia, Belgium, Canada, Greece, Iran, Kuwait, Mexico, New Zealand, South Africa, and the United Kingdom. Although the device had not been withdrawn from any market due to any reason related to the safety or effectiveness of the device, there have been 27 reports of serious adverse events during this commercial use. Approximately half of these reports included thermal injury to bowel in the absence of uterine perforation for which 11 patients needed bowel resection. These events, although rare, were of concern to FDA. The review of the PMA included a careful review of the events, including the patient and treatment factors that were thought to have contributed to them. For additional information on how these reports of adverse events during commercial use were handled during the review of the PMA, please refer to sections XIV and XV of this summary.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

The MEA System was evaluated in a randomized, prospective, multi-center clinical study, in which the MEA System was compared to a control arm of rollerball endometrial ablation (hysteroscopic endometrial ablation).

Tables 1 through 4 summarize the adverse events reported during the first year of follow-up for 324 patients entered in this study.

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. The use of pain medication was left to the discretion of the physician and patient.			

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.			

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 for 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

IX. SUMMARY OF PRE-CLINICAL TESTING

A. PERFORMANCE TESTING – DESIGN VERIFICATION

Microwave Connectors Pull Test: The "WW Fisher" and "N" type microwave connectors that are attached to the microwave module and the applicator assembly were both subjected to standardized Pull Testing to verify that the connectors can withstand accidental pull forces up to 100 N. The testing demonstrated there were no visual signs of damage or deformation to the connectors due to the pull tests.

Applicator Useful Life: Functional testing was performed and completed on 24 reusable Applicators. The testing consisted of repeated simulated uses which included soiling, cleaning and steam sterilization with standard procedures. The

results of the tests demonstrate that 92% (22/24) of the MEA Applicators remain functional after being subjected to 30 repeated uses.

Maximum Depth of Thermal Penetration (Worst Case Conditions): Design testing of the MEA System and Applicator was conducted to determine the maximum depth of thermal penetration associated with the use of the MEA System. Two computational models (steady-state and time-dependent) were developed to determine the worst-case depth of thermal penetration. These models have been spatially validated using polyacrylamide gel (PAG) and the resulting lesion sizes have been validated in porcine liver. In the worst-case scenario, which has been redefined to mean a stationary Applicator set at 90°C for a time interval of 8 minutes in non-perfused tissue, a maximum thermal penetration depth of 8.05 millimeters was determined.

Ex Vivo Testing: Bench testing with *ex vivo* porcine livers was completed to verify the shape and depth of heating caused by the microwave energy provided through the applicator tip at 9.2 GHz under simulated use conditions. Activation of microwave energy with the applicator completely surrounded by liver showed that a spherical uniform depth of coagulation, limited to 5-6 mm, was achieved.

MEA Applicator Shaft Temperature Testing: Testing was conducted to examine the temperature rise on the Applicator shaft. At the point along the shaft that is in contact with the patient's cervix, the temperature did not rise above 40 °C.

Temperature Rise Gate: Microsulis has validated a temperature rise gate (TRG), a temperature monitoring function of the software that identifies an abnormal temperature rise at the initiation of treatment.

Applicator Microwave Connector Leakage Testing: Far-field and near-field tests were carried out on the MEA applicator and N-type connector to provide assurance that the MEA applicator does not leak microwave energy at the surface and at distances less than 1 meter. The results of the testing demonstrate that the level of energy emitted from the MEA applicator is far below the safe limit specified for maximum continuous exposure as specified in IEEE C95.1. This confirms that there is no hazard to the clinician or the patient from far-field or near-field emissions from the MEA device.

Applicator Shaft Microwave Leakage Testing: Bench tests were conducted to confirm that the microwave energy radiation is confined to the tip of the applicator and not emitted along the entire length of the applicator shaft. A spatial peak value of specific absorption ration (SAR) was determined using a polyacrylamide gel phantom. Testing of the SAR around the applicator shaft using two thermocouples located 1 mm from the applicators N-type connectors detected no hazardous levels of SAR as defined by IEEE C95.1 (i.e., <8W/kg).

B. ELECTRICAL & MECHANICAL SAFETY; ELECTROMAGNETIC COMPATIBILITY

Electrical safety and electromagnetic compatibility testing was performed in accordance with internationally recognized standards by independent test facilities. Certification of Compliance and/or documentation of successful test results for the MEA System to the following standards was provided.

- EN 60601-1: electrical safety,
- IEC 60601-1-2: collateral standard, electromagnetic compatibility requirements of medical equipment,
- IEC 801-2: electrostatic discharge,
- IEC 801-3: radiated susceptibility,
- IEC 801-4: fast transient bursts,
- CISPR 11:990: radiated and conducted emissions,
- CFR 47 Part 18: FCC industrial, scientific and medical radiated emissions and
- CSA C22.2 601-1:Safety of medical equipment – part 1

C. SOFTWARE VALIDATION

In accordance with the requirements set forth in the FDA Guidance document entitled "*Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices*," the level of risk for the MEA System was considered to be **moderate**. The device hazard analysis provided takes into account the foreseeable hazards associated with the device's intended use, hardware and software and identifies the corrective measures taken to eliminate or reduce each hazard. Software documentation provided on the device system is consistent with its intended use, and the software level of concern and consists of the following:

- Device hazard analysis,
- Software description and requirements documents,
- Architecture design chart,
- Software traceability analysis, and
- Software validation results

The software validations demonstrated that the device and the software contained within the device perform in accordance with manufacturer's specification for the device and should function safely and effectively.

D. MATERIAL SAFETY (TOXICOLOGY)

Biocompatibility/Toxicity Testing

The polymer sheath that encapsulates the MEA Applicator sheath is the only device component that contacts the patient. Because the Applicator is a reusable device, the sheath was tested alone at time zero and the Applicator with the sheath encapsulating the shaft was tested after 30 simulated uses. The testing was

conducted in accordance with the requirements of International Standard ISO 10993: Biological Evaluation of Medical Devices, Part 1, and FDA's Good Laboratory Practices (GLP), 21 CFR 58, and included the following tests:

- Cytotoxicity (ISO Elution, MEM)
- Sensitization (ISO Maximization in the Guinea Pig)
- Irritation (ISO Acute Intracutaneous Reactivity in the Rabbit)

The sheath material passed the biocompatibility testing at both time zero and after 30 uses.

Sterility

The MEA Applicator is not supplied sterile. It is designed to be cleaned and sterilized by the user prior to use. The steam sterilization instructions recommended in the device labeling were validated by an independent laboratory to AAMI guidelines (AAMI TIR No. 12, 1994) and provide a sterility assurance level (SAL) for the device of at least 10^{-6}.

X. EXCISED UTERI STUDY

Ex vivo tests were conducted using the microwave applicator prototype on excised non-perfused and perfused uteri salvaged from routine hysterectomies to determine depth of necrosis, complete cavity coverage, serosal heating, and containment of all microwave energy in the uterine cavity. The endometrial cavities from 4 non-perfused extirpated uteri were ablated with power levels of 18 watts with varying "treatment" times of 360 seconds to 510 seconds. During these tests the temperature in the endometrial cavity and on the uterine body was monitored. Microwave leakage measurements were made using a power meter. All specimens were sent to pathology after treatment to measure coverage of ablated area and depth of necrosis using nitro-blue tetrazolium. The results of these tests showed that it was possible to destroy endometrial tissue throughout the uterine cavity to a limited depth of 5-6 mm without raising serosal uterine temperature levels.

Further experiments involved 8 extirpated uteri with simulated perfusion in which power levels were varied from 12-60 watts over 90 – 960 seconds. Temperature and microwave leakage measurements were made and the specimens were sent to pathology. The results of these tests indicated that "blood cooling" did not affect the depth of the necrosis and it was possible to destroy endometrial tissue throughout the uterine cavity without raising serosal uterine temperature levels. Varying power levels were evaluated to confirm that the physician could guide the applicator tip throughout the uterine cavity using tissue temperature measurements and reading to control coverage.

XII. SUMMARY OF CLINICAL STUDIES

A. PRE-HYSTERECTOMY CLINICAL STUDIES

In vivo tests were performed on 16 women prior to hysterectomy with power levels varying from 30 – 48 watts and 137 – 300 seconds. In each case the bowel was packed away and thermocouples were positioned on the uterine serosal surface to confirm that no temperature rise occurs during treatment. Following treatment, hysterectomy was completed and uterine specimens were sent to pathology.

Additional *in vivo* testing was completed on 3 subjects to evaluate the same parameters at the design power of 30 watts, and 40 watts to ensure no microwave leakage or serosal heating.

The *in vivo* testing provided valuable data regarding patient safety, the MEA surgical procedure, and the energy dose required to achieve a 5mm depth of destruction throughout the entire endometrial cavity. Internal uterine tissue necrosis was approximately 5-6 mm, while external serosal tissue and myometrium were undamaged.

B. FEASIBILITY & INTERNATIONAL CLINICAL STUDIES

Feasibility (Safety and Effectiveness) Study

A feasibility safety and effectiveness study of the MEA was conducted at the Royal United Hospital in Bath, England. The study began in October 1994 and included twenty-three women with menorrhagia. Average age was 42.6 years (range 36-55). Pre-treatment was either one injection of goserelin acetate (3-6 mg) or danazol (800 mg) four weeks prior to ablation treatment. Endometrial thickness was measured by vaginal probe ultrasound before treatment. Treatment was performed beginning with the fundal and cornual regions until the temperature at the tip of the probe reached 95 °C. There were no adverse events reported. After six months, success rate (defined as amenorrhea or light menstruation) was 83% (19/23). Thirteen patients (57%) were amenorrheic, and six patients (26%) experienced light menstruation. Four subjects were treatment failures. Three of these patients were retreated both medically and by MEA and became amenorrheic.

International Safety and Effectiveness Study

The first prospective, randomized, controlled clinical trial of the MEA System was conducted between September 1996 and February 1998 at Aberdeen Royal Infirmary, Aberdeen, Scotland. Of 263 women referred for endometrial ablation (on the basis of a subjective complaint of intolerable menstrual blood loss), 129 were randomized to MEA and 134 were randomized to transcervical endometrial resection (TCRE).

Primary endpoints were:

- satisfaction with procedure
- acceptability of procedure

Secondary endpoints were:

- effect on menstrual status
- health-related Quality of Life
- operative details
- morbidity

A total of 263 women were treated by endometrial ablation, 129 randomized to MEA, 134 to TCRE. Inclusion criteria were any patient experiencing heavy menstrual loss and referred for endometrial ablation by their physician, including the allowance of fibroids and irregular cavities in both the treatment and control arm.

Subjects received goserelin acetate (gonadotropin releasing hormone or "GnRH" analog) 3-6 mg approximately 5 weeks prior to treatment. Each clinical investigator had performed at least 50 TCRE procedures prior to study commencement. Each had also attended a training session to learn MEA and had performed at least 5 MEA procedures prior to study participation.

The mean cavity length was 7.4-7.5cm (±0.9) in both arms of the study. The rate of submucous fibroids > 2cm was 11-14%. Study results were very similar and favorable in both groups for all endpoints. The results were not statistically different for any endpoint. Seventy-five to seventy-seven percent of participants were totally or generally satisfied with treatment at 12 months. Ninety to ninety-four percent of participants found their treatment acceptable.

At 12-months post-treatment, 40% of the subjects in each group reported amenorrhea. Approximately 12-13% of subjects in each group reported that their period lasted 1-3 days. Eight to nine percent of subjects reported no improvement or a worsening of their menstrual status.

Four women in the MEA treatment group were unable to be treated with MEA because of equipment malfunction, and were instead treated with TCRE. One case of blunt perforation of the uterus with an inactive device occurred in each group. Four women in the MEA group were readmitted, three for "minor secondary hemorrhage that responded to antibiotic therapy." Six women were readmitted in the TCRE group.

The hysterectomy rate at 24-months was 11.6% for the MEA group and 12.7% for the TCRE group.

C. MULTI-CENTER CLINICAL INVESTIGATION

Study Objectives

The primary objective of the study was to evaluate the safety and effectiveness of the MEA System as compared to hysteroscopic rollerball endometrial ablation (REA) in reducing menstrual blood loss at 12 months post-treatment. An additional objective was to identify complications or adverse events that may occur using the MEA System. The two treatments were compared in a group of pre-menopausal women with menorrhagia (excessive uterine bleeding) from benign causes who no longer wished to retain fertility.

Study Hypothesis

The study hypothesis proposed a statistical difference of less than 15% in patient success rates at 1-year between MEA and REA.

Study Design

The study was designed as a prospective, randomized (2:1) controlled, multi-center (9 sites) clinical investigation to evaluate 324 pre-menopausal women with menorrhagia.

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 $\geq$185 pre-treatment to $\leq$75 at 1 year post-treatment. 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 Procedure Methods

Patient bleeding, the primary study endpoint, was documented by the subject in menstrual diaries which were scored by the clinical investigator or his/her designee to determine the amount of blood loss before and after treatment. The blood loss was scored using the validated scoring system. All patients were instructed to maintain menstrual diaries for 12-months post-procedure. All complications and adverse events were documented and reported. Protocol deviations and failures of the device to meet minimum performance criteria were also recorded. Quality of Life questionnaires were completed prior to treatment and at 3, 6 and 12 months post-treatment. As part of the study approval, questionnaires are to be completed at 24 and 36 months post-procedure as well.

Following determination of patient eligibility and obtaining Informed Consent, each patient was stratified by age (≤40 or >40 years of age) and randomized with a 2:1 ratio into either the MEA treatment group or the REA control group. 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 drug administration. Study subjects were required to meet the following inclusion/exclusion criteria:

Inclusion criteria

- Patient has abnormal uterine bleeding (AUB) as defined by excessive bleeding with a documented Pictorial Blood Loss Assessment Chart (PBLAC) score greater than or equal to 185, and previously had failed medical therapy (e.g., oral contraceptives or progestins) and who would have been offered endometrial ablative surgery or hysterectomy as a treatment for menorrhagia.

- Patients with previous diagnosis and failed, unable to tolerate, or refused medical therapy require 1 month (1 cycle) documentation

- Patients presenting to the study without documented failed medical treatment require 3 month (3 cycle) documentation, with a PBLAC average of > 185.

- Pre-menopausal at enrollment as determined by FSH measurement less than or equal to 30 I.U./mL and over 30 years old.

- Fit for general or local anesthesia.

- Not pregnant and no desire to conceive at any time.

- Patient agrees not to use hormonal contraception or any other intervention for bleeding during the study.

- Benign endometrium on preoperative endometrial sampling.
- Uterine sounding less than or equal to 14 cm

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 ensure 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 obstruct treatment access to any part of the endometrial cavity (as determined by hysteroscopy).
- Uterus sounds <6 cm.
- Previous endometrial ablative surgery.
- Previous classical cesarean section.
- Any portion of uterine wall measures <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 are pregnant or still desire 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

Study Period and Patient Population

The first patient was treated in April 2000 and the last patient was treated in September 2001. In addition to the one year follow-up required for PMA approval, all patients will be followed for an additional two years. (See section XV.)

A total of 324 patients were enrolled in the study in a 2:1 ratio (216 MEA, 108 control group of rollerball endometrial ablation.) One study site withdrew participation and the 2 patients (1 MEA, 1 REA) who had received treatment did not wish to continue in the study. These patients have been excluded from the effectiveness analyses. The intent-to-treat population for this study has been identified as a total of 322 patients (215 MEA, 107 REA).

Demographic and Gynecological History Data

Pre-procedure baseline demographics and gynecological history are summarized below in Table 5.

An evaluation of these data showed that 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 and, therefore, it was valid to compare treatment outcome.

Table 5 - Patient Demographics

Characteristic	MEA	REA	p-Value
N=	215	107	
Age			
Mean (years)	40.5	40.9	0.477
Std. Deviation (years)	4.58	4.57	
# of patients < 40 years	95 (44.2%)	44 (41.1%)	
# of patients > 40 years	120 (55.8%)	63 (58.9%)	
BMI (kg/m^2)			
Mean	27.97	27.01	0.250
Std. Deviation	7.10	6.61	
Race (# of patients)			
African-American	22 (10.2%)	12 (11.2%)	
Caucasian	187 (87.0%)	93 (86.9%)	
Other	6 (2.8%)	2 (1.9%)	
Baseline Diary Score			
Mean	451.84	524.60	0.109
Std. Deviation	356.59	429.53	
Uterine Cavity Length (cm)			
Mean	8.09	8.14	0.614
Std.Deviation	0.98	0.77	

All values, except race, are expressed in terms of mean ± standard deviation. All mean values, except BMI, are based on 215 MEA patients and 107 REA patients. BMI values are available for 204 MEA patients and 105 REA patients.

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.

Patient Accountability

A total of 324 patients were enrolled into the study. Table 6 identifies the numbers of patients at key points in the study.

Table 6 - 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	2	4	6
treatment*	1	0	1
Deceased (automobile accident)	1	0	1
Subject completed 12 month visit, started HRT month 9 (PBLAC invalid)	1	1	2
Subject completed 12 month visit, PBLAC lost			
Patients Evaluated Post-Op 12 Months (YTD)	194	96	290

*Includes 2 patients treated at McGill University which withdrew site participation. As discussed in Study Period and Patient Population, these patients were excluded from the effectiveness analyses.

Efficacy at One Year: Diary Scores

Patient success was based on a reduction in diary score from ≥185 pre-treatment to <75 at one year follow-up. Effectiveness rates were based on the intent-to-treat population.

Table 7 – Effectiveness*: Diary Scores at 1 year

	MEA n=215	**REA** n=107
Number of successful patients (diary score ≤75)	187	89
Study success rate (% patients with score ≤75)	**87.0%**	**83.2%**
Number of patients with amenorrhea (score = 0)	119	49
Amenorrhea rate (% patients with diary score = 0)	**55.3%**	**45.8%**

**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 the intent-to-treat effectiveness rates.*

Note: The effectiveness of MEA in treating menorrhagia patients who also had small cavity-distorting fibroids (≤3cm 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 8 - Effectiveness: Diary Scores at 1 year (Fibroid Analysis)

	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%**

Efficacy at One Year: 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 9 shows the patient responses at 12-months post-treatment. Percentages are calculated based on the number of responders (Evaluable Group).

Table 9 - Effectiveness: Quality of Life Data at One Year

	MEA N (%)	REA n (%)
Number of patients responding	196	97
Acceptance of operation		
Positive	194 (99.0%)	97 (100.0%)
Negative	2(1.0%)	0 (0%)
Overall treatment satisfaction		
Very satisfied / Satisfied	193 (98.5%)	96 (99.0%)
Dissatisfied	3 (1.5%)	1 (1.0%)
Dysmenorrhea		
Pre-treatment	176 (89.8%)	86 (88.7%)
Post-treatment	66 (33.6%)	33 (34.0%)

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.

Table 10 - Procedure Time

	MEA N=209	REA n=106	p-Value
Mean (minutes)	3.45	20.26	<0.001
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 groups. 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 this site.) 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.

Table 11 - 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 12 - 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 13 - Anesthesia Time

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

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. Subsequently she underwent a total abdominal hysterectomy, and bilateral salpingo-oophorectomy.

Device Failures and Replacements

Each US investigational site originally received one MEA System (V1 Console). Two investigational sites received a second MEA System (V2 Console) which contained modified software (Temperature Rise Gate). There were no reports of system failures during the trial period and no cases of device failure resulting in injury to a patient or a patient not being treated.

Forty-nine (49) applicators were used in the clinical study. There were 3 reports (6.1%) of minor procedural incidents with either a faulty applicator or difficulty in recognizing a connection of an applicator to the system. All procedures were completed in their entirety with only a minimal delay in treatment time not compromising patient safety. These issues have been addressed with minor modifications made to the system with the implementation of MEA System, Version 2. There was no case in which an applicator failure resulted in a patient injury or not being treated.

XIII. CONCLUSIONS DRAWN FROM THE STUDIES

The pre-clinical and clinical data provide reasonable assurance that the MEA System is safe and effective when used in accordance with the directions for use.

XIV. PANEL RECOMMENDATIONS

At a June 10, 2003, meeting of the Obstetrics and Gynecology Devices Advisory Panel Meeting, the Panel discussed the PMA (P020031) for the Microwave Endometrial Ablation (MEA) System. The panel discussed the results of the pivotal trial, adverse event data from commercial use of the MEA System, and the steps taken by the sponsor to mitigate the risk of these events.

As discussed in section VII, the commercial experience included 27 serious injuries that have been reported in non-U.S. commercial experience since 1998. Approximately half of these injuries included reports of bowel resection in the absence of uterine perforation. These adverse events were extensively discussed at this meeting. The Panel accepted the premise that the thickness of the myometrium played a significant role in these adverse events. In other words, if the uterine wall was too thin, transmyometrial thermal burns to the bowel could occur with this device. The mathematical modeling developed to provide some guidance on a safe minimum uterine wall thickness was discussed.

The sponsor described the steps taken to minimize the risk of such adverse events including retraining the physicians who were already using the device commercially outside the U.S. and instituting additional patient selection criteria and pre-operative procedures.

The panel was reassured that out of approximately 5000 MEA cases performed since November 2002, when the sponsor had instituted some of these changes, there had been no new reports of serious patient injury.

The panel accepted that the mitigating measures put into place by the sponsor before November 2002 in combination with the requirement for an appropriate minimum myometrial thickness would have the intended result of reducing the risks associated with MEA.

At the conclusion of the deliberations, the Panel recommended that the PMA (P020031) for the MEA System be approved with the following conditions:

1) New users will undergo training and preceptorship.
2) Mechanical endometrial thinning (e.g. D&C) will not be allowed for this procedure.
3) All patients will have hysteroscopic examination after dilatation.
4) All patients must have a minimum myometrium thickness of 10 mm throughout the uterus, as measured by ultrasound; measurements will include the cornua; ideally, transvaginal ultrasound will be used.
5) Users will be required to have experience in diagnostic hysteroscopy.

6) The labeling will be modified to reflect the above clinical requirements.
7) There will be a statistical analysis for non-inferiority, including confidence intervals, based on the true intent-to-treat groups.

XV. FDA DECISION

FDA concurred with the Panel's conclusions with the exception of the requirement for physician preceptorship. The applicant's training program will include preceptoring of new users for a minimum of 3 treatments conducted either by a physician or by Microsulis-certified clinical personnel.

Although FDA concurs with the recommendation for a minimum myometrial thickness of 10mm, this agreement was reached after the panel meeting based on additional engineering and clinical review. This review resulted in the requirement for the following changes:

1. FDA and the sponsor agreed on an acceptable mathematical model for predicting thermal penetration with the MEA System under worst case conditions, i.e., no uterine perfusion and an Applicator tip temperature of 90 °C at a fixed location for the duration of the treatment. Reducing the maximum treatment time from 12 minutes to 8 minutes lowered the model's prediction of thermal penetration from 9.00 mm to 8.05 mm. (This is still approximately 4 minutes longer than the typical procedure.) An additional 2 mm was added to account for the measurement uncertainty of ultrasound, and this, in turn, led to the 10 mm minimum myometrial thickness requirement now specified in the labeling.

2. A formal ultrasound protocol was developed with help from additional consultants to FDA. This ultrasound is used to determine the depth of myometrial thickness especially at the thinnest portion of the myometrium, i.e., the uterine cornua and the lower uterine segment. Due to the unknown effects of short-term suppression of myometrium, it was determined that in addition to the ultrasound examination performed at screening, a second vaginal ultrasound should be performed not more than 10 days before the MEA treatment in the following patients:

   - 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, the physician is instructed not to perform the MEA treatment.

- 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.

- Patients who have received more than one 30-day dose of GnRH therapy

In considering the changes made to labeling and training to improve the safety of the MEA System, FDA asked the sponsor to take actions in the post-market setting to confirm that these measures were sufficient. In order to enhance the reporting of potential adverse events associated with the MEA System, Microsulis agreed to collect information on hospital readmissions, unanticipated office visits and unscheduled diagnostic or exploratory surgical procedures, within 90 days of an MEA treatment. This information will be obtained from the Physician Report Forms developed as part of the approved training plan and from the Patient Treatment Card. Microsulis agreed to provide FDA with quarterly reports which contain the number of reports received as well as the number of procedures conducted within the reporting interval. This will be required until a total of 3000 procedures have been performed in the U.S.

In order to gather long-term safety and effectiveness data, the applicant must conduct a post-approval study that will continue to follow all subjects from the multi-center study for a period of three years from the time of treatment.

Finally, Microsulis revised the labeling in keeping with the recommendations of the Panel and the additional changes imposed by FDA.

Additionally, CDRH found the applicant's manufacturing facilities to be in compliance with the device Quality System Regulation (21 CFR 820). CDRH issued an approval order on September 23, 2003.

XVI. APPROVAL SPECIFICATIONS

Directions for use: See the labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, precautions and Adverse Events in the labeling.

Postapproval Requirements and Restrictions: See approval order.