

## **SUMMARY OF SAFETY AND EFFECTIVENESS DATA**

### **I. GENERAL INFORMATION**

<b><u>Device Generic Name :</u></b>	(Hysteroscopic) Thermal Endometrial Ablation Device
<b><u>Device Trade Name :</u></b>	Hydro ThermAblator® Endometrial Ablation System
<b><u>Applicant's Name and Address:</u></b>	BEI Medical Systems Company, Inc. 100 Hollister Road Teterboro, New Jersey 07608
<b><u>Premarket Approval Application (PMA) Number:</u></b>	P000040
<b><u>Date of Panel Recommendation:</u></b>	None
<b><u>Date of Notice of Approval to Applicant:</u></b>	April 20, 2001

### **II. INDICATIONS FOR USE**

The Hydro ThermAblator® System (hereinafter called the HTA® System) is a hysteroscopic thermal ablation device intended to ablate the endometrial lining of the uterus in premenopausal women with menorrhagia (excessive uterine bleeding) due to benign causes for whom childbearing is complete.

### **III. CONTRAINDICATIONS**

The use of this device is contraindicated in a patient:

- who is pregnant or wants to be pregnant in the future, because pregnancy after ablation can be dangerous to both mother and fetus;
- who has known or suspected endometrial carcinoma (cancer) or premalignant change of the endometrium, such as, adenomatous hyperplasia;
- who has active pelvic inflammatory disease or hydrosalpinx;
- who has any anatomical pathologic condition in which weakness of myometrium could exist, such as, prior classic cesarean section or transmural myomectomy;
- who has an intrauterine device in place; or
- who has active genital or urinary tract infection, e.g., cervicitis, endometritis, vaginitis,

cystitis, etc., at the time of treatment.

#### IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the HTA® Installation and Operator's Manual.

#### V. DEVICE DESCRIPTION

The HTA® System is a hysteroscopic, software-controlled, thermal endometrial ablation system that consists of (a) an operational unit, (b) a heater canister, and (c) a sterile procedure set. The system also requires the use of USP 0.9% saline and a standard hysteroscope. The following is a pictorial representation of the HTA® System:

**Figure 1 - HTA® System**



**HTA® System**



**Sheath Assembly**

The device is a closed loop system designed to ablate the endometrial lining of the uterus by recirculating heated saline within the uterus. The saline is heated to a temperature of 90 °C by a heating element located in the external heater canister, fed to the uterus by gravity and recirculated via an aspiration pump. The system includes various alarms and sensors to monitor the 10-minute treatment cycle.

### **(a) Operational Unit**

The operational unit contains the hardware and software components which facilitate and control the safe operation of the HTA® System. These components include the user interface display and control buttons, fluid pump and valves, power connection, cabinet, and IV pole. The user interface provides instructions to guide the user through the phases of the ablation procedure.

Fluid management throughout the system is controlled by a peristaltic pump and series of valves. The pump aspirates fluid from the uterus and into the fluid reservoir chamber in a continuous manner. Valves are used to enable and prevent fluid flow within the system during various phases of the procedure.

The system is supplied with a power cord which provides an input voltage of 95-135 VAC at 50/60 MHz, with a maximum current of 15 amps.

### **(b) Heater Canister**

The heater canister is the plastic (polycarbonate) chamber within which circulating fluid is heated prior to delivery to the uterus. The canister houses two redundant thermistors and an electrical connection to the operational unit. This connection allows the thermistors to continually measure the temperature of the heater canister in real-time.

The canister consists of a two-layered cylinder within which is housed the heating element, thermistors and O-ring sealant. The two layers of the cylinder are separated by an air barrier, which helps minimize the temperature of the outer surface of the canister. As the fluid within the inner cylinder reaches temperatures up to 90°C during treatment, the outer plastic cylinder mitigates the likelihood of thermal injuries to the operator in the event of direct contact with the canister. The heating element is a metal rod which is mechanically connected to the base of the cylinder and electrically connected to the operational unit. The O-ring provides a seal to prevent fluid from escaping from the inner cylinder of the canister.

The heater canister is intended for multiple uses. It is provided non-sterile and is designed to be cleaned and then resterilized via autoclave. The specific method for reprocessing has been fully described and validated.

### **(c) Sterile Procedural Set**

The sterile procedural set consists of a patient sheath, tubing lines, cassette, fluid level measurement reservoir, and fluid collection bag. The kit is provided sterile for single use.

The patient sheath, constructed of polycarbonate, contains two concentric lumens to allow for continual fluid flow and provides thermal insulation. The outer diameter of the sheath is 7.8 mm. The cervix is dilated to approximately 8 mm in order to accommodate the sheath. The proximal end of the sheath is attached to a standard 3 mm hysteroscope, which provides real-time visualization of the ablation procedure.

The tubing lines provide connections between the sheath, operational unit (peristaltic pump), and fluid reservoir. The tubing segment between the pump and sheath features an

insulating, corrugated tubing line which acts to prevent accidental burn to the patient or operator, in the event that the patient/operator contacts the tubing line while it is heated.

The cassette is loaded onto the cassette plate of the operational unit. The casing of the cassette contains five contact points where the unit valves of the unit are actuated. The casing also provides the track which houses the tubing line for the pump segment.

The fluid level measurement reservoir consists of a cylinder that is connected to the IV pole of the operational unit. The transparent face of the reservoir features fluid level markers which display the net fluid status throughout the procedure in the closed loop system. The reservoir electronically tracks changes from the 80 mL normal operating fluid level by means of an electronic strip with fluid sensors and will alarm when it senses a loss of 10 mL or an increase of 20 mL.

### **Principle of Operation**

Once the treating physician determines that a patient is an appropriate candidate for the ablation procedure with the HTA®, the patient should be given a dose of medication (e.g., Lupron) to thin the lining of the uterus approximately three weeks prior to the procedure. (However, the optimum pre-treatment regimen has not been established.)

At the time of the procedure, the components of the HTA® are assembled and connected to a standard hysteroscope. The patient receives some combination of anesthesia/analgesia at the discretion of the physician. A bimanual examination of the uterus is performed. A vaginal speculum is inserted, a tenaculum is placed on the cervix, the cervix is dilated to 8 mm and then the patient sheath is introduced through the cervix and positioned in the uterus.

The ablation procedure consists of a series of steps which are guided by the software and user interface of the HTA®. During the initial priming phase, when the uterine cavity is inspected, room temperature saline circulates within the system and uterus at a flow rate of approximately 300 mL/min for 2 minutes. The active treatment phase follows, at which time the HTA® heating element activates and begins to elevate the temperature of the saline. When the saline temperature reaches 80°C, the treatment period of 10 minutes is started. The saline temperature continues to elevate, until it reaches 90°C, and remains there for the duration of the active treatment phase. Fluid flow through the system is approximately 300 mL/min.

The HTA® is designed with components and alarms to monitor the safe delivery of saline and may interrupt treatment therapy if an unsafe state is detected. After the entire 10-minute treatment cycle is successfully completed, the treatment proceeds to the post-treatment flush phase. Room-temperature saline is flushed through the uterus to rapidly reduce the temperature of the fluid in the uterus and sheath. In the event of interruption of the procedure prior to completion of the 10-minute treatment phase, the system will proceed to the same cooling cycle as stated above. After approximately one minute, the physician removes the sheath from the patient. The procedure is terminated at this time. The unit then

proceeds to a final system cool-down phase, during which the room-temperature saline continues to circulate through the system for an additional period of time until the temperature of the fluid in the heater canister reaches 45 °C.

## **VI. ALTERNATIVE PRACTICES OR PROCEDURES**

The following alternate 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 are most often employed for the treatment of menorrhagia. Other classes of drugs used include androgens such as danocrine, GnRH agonists, non-steroidal anti-inflammatory drugs (NSAIDs). Drug therapy is typically the first order treatment to alleviate menstrual symptoms. Drug therapies usually require long term treatment. They are successful for some patients but for others they are ineffective and often introduce unpleasant side effects. This treatment, however, does 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. 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 but it is useful for those women who desire to maintain their fertility. D&C is also useful as a diagnostic technique to rule out endometrial cancer.

- **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. Dilation of the cervix must accommodate the hysteroscopic instrument, usually to a minimum of 9 mm and the uterus must be properly distended. The most common risks associated with hysteroscopic endometrial ablation are fluid overload, and perforation. This treatment is intended for women who no longer desire to maintain their fertility.

- **Thermal Balloon Ablation**

The ThermaChoice™ Uterine Balloon Therapy™ (UBT) System is a software controlled device designed to ablate endometrial tissue by thermal energy heating of sterile injectable fluid (5% dextrose in water) within a silicone balloon. The ThermaChoice™ UBT System consists of a controller with power cord, single-use sterile catheter, and umbilical cable. During the treatment, the fluid within the

balloon is circulated via an impeller to maintain a temperature of 87°C for a period of 8 minutes. This treatment is intended for women who no longer desire to maintain their fertility.

- **Cryosurgical Ablation**

The HerOption™ Uterine Cryoablation Therapy™ System is a software-controlled, cryoablation system that consists of a console, cryoprobe, and control unit. The device generates extremely cold temperatures by means of pressurized gas, consisting of a mixture of common refrigerants, that is expanded through a small orifice in the cryoprobe. Deployment of the pressurized gas forms an iceball, whose leading (outer) edge reaches temperatures sufficient to destroy tissue (-20°C). In the procedure, the probe is angled toward one cornua (side) of the uterus for a period of 4 minutes during which the first iceball is formed; the probe is then angled to toward the other cornua for a period of 6 minutes during which the second iceball is formed. Use of the device must be accompanied by ultrasound to enable visualization of the cryoprobe tip placement and the leading edge of the iceball. This treatment is not intended for a woman who desires to maintain her fertility.

- **Hysterectomy**

The most common surgical procedure, hysterectomy, is a definitive treatment for excessive menstrual bleeding. It is, however, a major surgical procedure performed in the hospital under general anesthesia that is associated with risks and complications and generally a lengthy recovery period.

## **VII. MARKETING HISTORY**

The HTA® System has been commercially marketed internationally since January 1996. At time of FDA approval, the HTA® System was available in 22 countries and not withdrawn from the market for any reason relating to the safety and effectiveness of the device.

## **VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH**

Adverse effects of the device on health may be categorized as those observed during the clinical evaluation of the HTA® System and those not observed in the study, but which may occur.

### **(a) Adverse Effects of the Device on Health**

The HTA® System was evaluated in a randomized, prospective, multi-center clinical trial, comparing the HTA® System (HTA®) to roller ball (RB) ablation. Adverse event data were available from a total of 269 subjects treated in the study, from the time of procedure through the 1-year follow-up study period.

The tables below describe these results:

**Table 1a -- Adverse Events within 24 hours Post-Procedure**

<b>Adverse Event</b>	<b>HTAÒ Group n=184</b>	<b>RB Group n=85</b>
uterine cramping	51 (28%)	21 (25%)
nausea	20 (11%)	2 (2%)
vomiting	20 (11%)	2 (2%)
abdominal pain	8 (4%)	2 (2%)
urinary tract infection	5 (3%)	2 (2%)
laceration	2 (1%)	2 (2%)
endometritis	2 (1%)	1 (1%)

**Table 1b -- Adverse Events at 2 week Post-Procedure**

<b>Adverse Event</b>	<b>HTAÒ Group n=184</b>	<b>RB Group n=85</b>
uterine cramping	37 (20%)	11 (13%)
transient change in appearance of cervical epithelium	19 (10%)	0 (0%)
vomiting	17 (9%)	2 (2%)
nausea	16 (9%)	4 (5%)
abdominal pain	6 (3%)	0 (0%)
urinary tract infection (UTI)	3 (2%)	0 (0%)
endometritis	1 (1%)	1 (1%)
thermal injury to extremity	1 (1%)	0 (0%)
vaginal infection	1 (1%)	0 (0%)
cervical laceration	1 (1%)	0 (0%)

**Table 1c -- Adverse Events at 3, 6, and 12 months Post-Procedure\***

<b>Adverse Event</b>	<b>HTAÒ Group n=184</b>	<b>RB Group n=85</b>
uterine cramping	25 (14%)	8 (9%)
vaginal infection	6 (3%)	2 (2%)
nausea	3 (2%)	0 (0%)
vomiting	3 (2%)	0 (0%)
abdominal pain	2 (1%)	1 (1%)
hematometra	1 (1%)	2 (2%)
urinary tract infection	1 (1%)	1 (1%)

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

Additional information related to some of these events is provided below:

- **Peri-operative uterine cramping** - This event typically lasted a few days following ablation. Use of NSAIDs prior to and following HTA® treatment was usually sufficient to manage cramping.
- **Nausea and Vomiting** - These events were generally attributed to certain types of general anesthesia.
- **Asymptomatic Alterations in Cervical Tissue** - This type of event ranged from erythema to shallow ulcerations and was resolved without treatment within 30 days following ablation.
- **Endometritis** - This event was resolved with antibiotics in all subjects.
- **Hematometra** - This event was resolved with insertion of a uterine sound.
- **Thermal Injury to Extremity** - This event, consisting of a second-degree burn, occurred following prolonged exposure of skin (lower leg) to the heated tubing of the HTA® during treatment. The subject was treated with topical antibiotics and dressing changes. The device was modified after the occurrence of this event to reduce this risk of injury.
- **Other Events** - Other events, which occurred in no greater than 3% of subjects treated with the HTA®, included: diarrhea, fever, headaches, abdominal distension, and post-ablation tubal sterilization syndrome.

**(b) Potential Adverse Effects of the Device on Health**

The following adverse effects may potentially occur, but were not observed in clinical studies of the HTA®:

- thermal injury to adjacent tissue;
- heated saline escaping from the device system into the vascular spaces, cervix, or abdominal cavity;
- hemorrhage;
- perforation of uterus;
- complications with pregnancy (**NOTE:** pregnancy following endometrial ablation is dangerous to both the mother and the fetus); and
- risks associated with hysteroscopy.



## **IX. SUMMARY OF PRE-CLINICAL TESTING**

### **A. THERMODYNAMIC MODELING**

- (1) Sheath Test - The purpose of the sheath test was to verify the sheath design specifications (e.g., temperature on surface, flow rate) in a simulated environment. In this test, thermocouples were placed on the surface of the sheath, which was wrapped in chicken breast. A simulated procedure was performed while the sheath temperature was measured. Test results showed that the temperature reached a peak of approximately 42°C after 320 seconds of the procedure. A flow meter documented that the inflow and outlet flow rates were 0.7 L/min and 3.2 L/min, respectively.
- (2) Temperature versus Time: Warm-up and Ablation Phase - The purpose of this test was to evaluate the rate at which the temperature of the fluid increased from room temperature (approximately 22°C) to ablation temperature (90°C). In this test, a simulated treatment was performed while the fluid temperature within the heater canister was monitored. Results showed that the system took approximately 150-180 seconds to reach ablation temperature.
- (3) Temperature versus Time: Heater Canister Temperature - The purpose of this test was to measure the temperature of the inner and outer surfaces of the heater canister during the treatment period. In this test, a simulated 10-minute treatment was performed while the inner canister surface was measured with thermocouples and the outer canister surface was assessed by human touch. Results showed that the inner canister surface remained at 90°C during the complete treatment period and that outer canister surface may be contacted by an individual without discomfort.
- (4) Temperature versus Time: Cooling Cycle - The purpose of this test was to determine the rate at which the temperature reduced after termination of the active ablation procedure. In this test, a simulated treatment (including post-treatment phase) was performed while the temperature inside the heater canister was measured. Results showed that upon completion of treatment, circulating fluid was cooled to body temperature in approximately 20 seconds. As a result of these findings, the HTA® was designed to have a 1-minute cool down phase before the physician is instructed to remove the sheath from the patient.
- (5) Simulated Fluid to Patient Temperature - The purpose of this test was to determine the temperature differential between the fluid in the heater canister, where heating is initiated, and the fluid upon contact to the patient. In this test, temperature measurements at the canister and sheath were obtained. Results showed that the temperature of the fluid dropped approximately 3 to 4°C from the canister to the catheter. These findings characterize the heat sink effect in which fluid at an elevated temperature tends to drop to the temperature of the

surrounding environment. As a result of this phenomenon, the device was designed to provide rapid circulation of fluid during the ablation procedure, in order to better ensure that fluid heated to 90°C contacts the uterus.

## **B. BIOCOMPATIBILITY**

Biocompatibility information was supplied to provide assurance that the patient-contacting materials of the HTA® were safe for use in a medical device. The HTA® contains components which may be categorized as those which provide direct contact to patient tissue (e.g., patient sheath catheter) and those which contact the fluid flow path which comes into contact with patient tissue (e.g., canister, tubing lines).

To support the biocompatibility of the polycarbonate material, the sponsor submitted the results of these tests:

- cytotoxicity (USP 23 "Elution Cytotoxicity test") - sheath catheter, fluid pathway
- sensitization (ISO 10993-10 "Maximization sensitization test") - sheath catheter, fluid pathway
- intracutaneous reactivity - sheath catheter
- intracutaneous injection (USP 23) - fluid pathway
- systemic injection (USP)- fluid pathway
- hemolysis (rabbit blood)- fluid reservoir

Results submitted for these tests demonstrated that the test material device successfully passed each test.

In addition to these tests, the sponsor conducted leach testing on internal fluid pathway of the device system. During clinical use, device components that contact the internal fluid pathway are exposed to temperatures of up to 90°C, a state which may elicit the release of leachables. In this test, the sponsor operated the system such that fluid was circulated at 90°C for 2 hours. Extractions were obtained and analyzed via Fourier Transform Infrared (FTIR) spectroscopy for presence of unknown leachables. Results did not identify any unknown leachables in the product extract.

## **C. STERILITY**

The procedural set is supplied sterile and intended for single use. The heater canister is not supplied sterile. It is designed to be cleaned and sterilized by the end user and is intended to be reused.

The procedural set is sterilized with 100% ethylene oxide (EtO) to a sterility assurance level of  $10^{-6}$ . The sterilization process is validated in accordance with ANSI/AAMI/ISO 11135-1994. Maximum residual level of EtO, ethylene

chlorohydrin, and ethylene glycol were identified as 25, 25 and 250 parts per million, respectively.

The heater canister is a reusable component. (The number of reuses is specified in the device labeling.) The canister must be cleaned with warm water and a mild soap using an appropriate brush or cloth. The canister must be autoclave sterilized with either a flash method (270°C for four minutes) or wrap method (250°C for the length of time appropriate for sterilizer load and components of load, consistent with hospital guidelines). Adequate validation of the protocols for reprocessing was supplied.

The shelf life of the procedural set was established at two years. This duration was based on real-time evaluation of product, in which aged product was subjected to sterility/package integrity and functional testing.

#### **D. ELECTRICAL SAFETY/ELECTROMAGNETIC COMPATIBILITY**

Electrical safety and electromagnetic compatibility testing was performed in accordance with the following standards by an independent test facility:

- EN 60601-1: electrical safety
- UL 2601-1: electrical safety
- CSA 22.2 No. 601-1 (safety of medical electrical equipment - part 1)
- EN 60601-1-2: collateral standard, electromagnetic compatibility requirements of medical electrical equipment
- IEC 801-2: electrostatic discharge requirement
- IEC 801-2: radiated susceptibility
- IEC 801-4: conducted transient susceptibility
- EN 55011B/CISPR 11: emissions limits for medical RF equipment
- IEC 801-5: surge immunity

Certification of compliance of the HTA® to these standards was provided.

#### **E. SOFTWARE VALIDATION**

In accordance with the FDA document "Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices," the level of risk of the HTA® was considered to be **moderate**, as the software contained in the device controls delivery of thermal energy, which, if not properly controlled, may cause injury to the patient. The hazard analysis and documentation submitted on the device system reflect this level of risk and consist of the following documents:

- system specification requirement plan;
- software requirement specification;
- software validation plan;
- software test plan;

- software test results;
- architectural design chart;
- traceability matrix; and
- hazard and failure mode effects analysis.

Test results demonstrated that the device performed in accordance with the specifications defined for the device. Based on these results, the software contained in the device should function safely and effectively.

## **F. ANIMAL TESTING**

Animal testing was performed in a series of two studies conducted on porcine models. The objective of these studies was to evaluate the safety and feasibility of the device for use in the human uterus. In particular, the studies allowed assessment of two characteristics of the device's principle of operation: (1) target and non-target tissue temperature exposure; and (2) effect of uterine circulation on temperature dissipation. A porcine model was chosen because of similarities to the human cervix and uterus, including the approximate thickness of cervix and uterine blood supply.

### **Initial Study**

Two pigs were used in this study. A laparotomy was performed, the cervix and uterus were exteriorized, and ligatures were placed at the vagina and uterine horns to isolate section of tissue to be tested. Thermocouples were placed in each pig in the uterine lumen (target tissue) and on the cervical serosa (non-target tissue). Saline was heated to approximately 85°C and cycled through the isolated uterine space through insulated tubing and inflow channel of the hysteroscope. Heated saline was allowed to flow by gravity for three minutes, during which uterine and serosal temperatures were measured. Tissues were examined histologically and histochemically to assess nuclear destruction and depth of tissue necrosis. Results showed that internal uterine temperature ranged from 71 - 81°C and external serosal temperature ranged from 38 - 43°C. Internal uterine tissue necrosis was approximately 4 mm, while external serosal tissue and uterine myometrium were undamaged.

### **Follow-up Study**

Two pigs were used in this study. Thermocouples were placed in uterine tissue, superficial myometrium, peripheral myometrium and serosa. Saline was heated to approximately 85°C and introduced in the same manner as the initial study. Treatment time was 3 minutes for the first pig and 8 minutes for the second pig. Measurements were taken at 3 minutes (both animals) and 5 and 8 minutes (second pig only). Tissues were examined macroscopically and microscopically. Results showed that temperatures at 3 minutes ranged from 68 - 76°C for uterine tissue, 64 - 66°C for superficial myometrium, 38 - 47°C for peripheral myometrium, and 24 - 36°C for serosa. At 5 minutes, target tissues ranged from 68 - 76°C and non-target tissue were 48°C or lower. Gross visual examination, histology and histochemistry indicated tissue necrosis in the endometrium and superficial myometrium (5 mm) with no evidence of necrosis in the peripheral myometrium or serosa at 48 hours. Overall findings from the studies demonstrated that introduction of heated saline induced

tissue necrosis within the target tissue without concomitant necrosis of non-target tissue.

## **X. SUMMARY OF CLINICAL STUDIES**

Clinical evaluation of the HTA® System was conducted in studies categorized as Phase I (feasibility safety), Phase II (feasibility safety and effectiveness), and Phase III (pivotal safety and effectiveness). These studies are described below.

### **A. Phase I (Feasibility Safety) Study**

Phase I (feasibility safety) testing of the device evaluated the preliminary safety of heated, free-flowing saline as a medium to thermally ablate the endometrium in pre-menopausal women with excessive uterine bleeding. This testing was conducted in a series of three stages, which are described below.

#### First Stage

The purpose of the first stage was to evaluate (1) the concept of free-flowing saline as a medium for ablation and (2) the design of the HTA® in the control of potential fluid loss through the fallopian tubes. A total of four subjects, who were scheduled for tubal ligation, received a mock ablation procedure with unheated, dyed saline. The procedure was observed via laparoscopy. In all procedures, no fluid loss alarms were triggered by the machine and no fluid loss through the fallopian tubes was observed with the laparoscope.

#### Second Stage

The purpose of the second stage was to investigate the treatment parameters (i.e., temperature of saline and time of procedure) of HTA® ablation. Twenty-four subjects were enrolled in this stage. Enrolled study subjects received the ablation procedure and then underwent a laparoscopic-assisted hysterectomy. The ablation procedure was completed on 16 of 24 subjects. Treatment times ranged from 3-8 minutes and treatment temperature was approximately 85°C. Histological data available from 11 of 16 subjects documented that depth of destruction ranged from 1 to 3 mm. In addition, complications with the procedure (e.g., fluid leakage, heater canister leakage) resulted in modifications to the device.

#### Third Stage

The purpose of the third stage was to investigate the treatment parameters of the HTA® that contained design modifications made in response to observations from the second stage. Nine subjects were enrolled. The ablation was completed on 8 of 9 subjects. Treatment times ranged from 4-6 minutes and treatment temperature was approximately 85°C. Results demonstrated that the modified device appeared to perform safely.

## **B. Phase II (Feasibility Safety and Effectiveness) Study**

Phase II (feasibility safety and effectiveness) testing of the device evaluated safety and preliminary effectiveness of heated, free-flowing saline as a medium to thermally ablate the endometrium in pre-menopausal women with excessive uterine bleeding. This testing was conducted in two stages.

### First Stage

The first stage of Phase II testing was conducted outside the United States. Its purpose was to investigate the effectiveness of the device with several different treatment parameters (e.g., treatment times ranged from 5 to 10 minutes, and treatment temperatures ranged from 85°C to 90°C). Twenty-five subjects were enrolled in these studies. Treatment effectiveness and adverse event information was documented. Results showed that ablation performed with saline at 90°C for a period of 10 minutes was as safe and potentially more effective than ablation performed at lower temperature and shorter treatment times, based on a level of destruction of the endometrium to 4 mm.

### Second Stage

The second stage of Phase II testing was conducted in the United States. Its purpose was to investigate the effectiveness of the device with saline heated to 90°C at a total treatment time of 10 minutes. Twenty subjects were enrolled in this study. Study subjects had a baseline bleeding diary score of at least 150 (adapted from *Janssen CAH, Scholten PC, et al. based on "A Simple Visual Assessment Technique to Discriminate Between Menorrhagia and Normal Menstrual Blood Loss". Obstetrics & Gynecology, Vol. 85, No. 6, June 1995*). No adverse events were reported. Of the 19 subjects for whom 6-month post-treatment information was available, 14 reported bleeding diary scores within normal levels (=75). Results demonstrated that the device, when used with treatment parameters of 90°C for 10 minutes, provided preliminary evidence of safety and effectiveness in treatment of excessive uterine bleeding.

## **C. Phase III (Pivotal Safety and Effectiveness) Study**

Phase III testing was conducted in the United States. This pivotal safety and effectiveness study was a multi-center, randomized, concurrently-controlled clinical trial in which subjects were randomized between the test device (HTA®) and the control device (roller ball [RB]) at a 2 to 1 ratio.

### **Objective**

The objective of the study was to assess the safety and effectiveness of HTA® ablation, relative to RB ablation in terms of safety and effectiveness in the treatment of patients with menorrhagia due to benign causes in an anatomically normal uterine cavity.

## **Study Endpoints**

The primary effectiveness endpoint was the *Janssen* diary scoring system (see above reference). Treatment success was defined as reduction in menses to a diary score of  $\leq 75$  in order to assure a return to eumenorrhea. Overall study success was a statistical difference of  $< 20\%$  in the success rate between HTA® and RB in the reduction of excessive menstrual bleeding to at least normal levels. Secondary effectiveness endpoints evaluated were overall percent decrease in diary scores and responses from a quality-of-life questionnaire. Safety endpoints were adverse events associated with each procedure, including device-related complications, time of procedure, and type of anesthesia used.

## **Study Methods**

A randomized, prospective, multi-center clinical investigation was conducted at nine sites using investigators experienced with hysteroscopic roller ball endometrial ablation. Prior to acceptance in the study, subjects underwent a series of screening examinations which primarily documented bleeding status and uterine structure. Demographic information and gynecological history was recorded. Subjects were required to meet a set of entry criteria.

### Inclusion Criteria

Subjects were enrolled in the study if they had the following:

- excessive uterine bleeding, as documented by the menstrual diary and calculation worksheet defined by Janssen (with a minimum score of 150);
- endometrial cavity measuring  $\geq 10.5$  cm;
- age  $\geq 30$  years; and
- previously failed, did not tolerate, or refused medical therapy.

### Exclusion Criteria

Subjects were excluded from the study if they had the following:

- age  $> 50$  years;
- active or recurrent chronic pelvic inflammatory disease;
- active genital or urinary tract infection;
- clotting defects, bleeding disorders, or anticoagulant treatments;
- abnormal pap smear that showed evidence of dysplasia;
- malignant pathology and/or simple hyperplasia, as documented by endometrial biopsy;
- history of gynecologic malignancy within the past 5 years;
- submucous myomas and/or polyps;
- intramural fibroids  $> 4$ cm, as documented on ultrasonogram, thought to be contributing to menorrhagia, such as those deforming the uterine cavity;
- congenital uterine anatomical anomaly, such as full septate or bicornate uterus;
- previous endometrial ablation procedure;
- previous classic Cesarean section;
- current pregnancy or desire for future pregnancy;
- desire for complete amenorrhea; and
- known hydrosalpinx.

Subjects received one dose of Lupron 7.5mg on Cycle Day 21 ± 2 days. Treatment took place on Cycle Day 19 - 27 after injection. After completion of treatment, subjects were followed at 2 weeks, and 3, 6, and 12 months post-treatment.

### Description of Subjects

Two hundred seventy-six subjects were enrolled in the study. Baseline demographic and gynecological variables were statistically equivalent between the two groups with regard to age, race, body mass index, mean baseline diary score and other criteria. The table below summarizes some key demographic information and gynecological history on study subjects:

**Table 2 -- Demographics and Gynecological History<sup>†</sup>**

<b>Baseline Characteristics/Gynecological History</b>	<b>HTA®</b>	<b>RB</b>
Race		
Caucasian	84%	76%
African-American	15%	19%
Other	2%	5%
Age (years)	40.7 ± 5.2	40.6 ± 5.3
Body Mass Index (BMI kg/m <sup>2</sup> )	29.0 ± 7.4	28.8 ± 7.8
Baseline Diary Scores	596.6 ± 787.6	585.5 ± 565.2
Hemoglobin (g/mL)	12.6 ± 1.3	12.5 ± 1.7
Hematocrit	37.4 ± 3.3	37.6 ± 4.3
Uterine Sound Length (cm)	8.5 ± 1.3	8.6 ± 1.2

<sup>†</sup> All values, except for race, are expressed in terms of mean ± standard deviation.

### Subject Accountability

The table below describes the accountability of subjects throughout the study period.

**Table 3 -- Subject Accountability**

<b>Subjects:</b>	<b>HTA®</b>	<b>RB</b>	<b>Total</b>
enrolled in study	187	89	276
received no treatment	3	4	7
received incomplete treatment	7	0	7
for whom 12-month data not available:	10	2	12
received hysterectomy <sup>†</sup>	2	0	2
died in non-device-related events	2	0	2
lost to follow-up	6	2	8
for whom 12-month data available	167	83	250

<sup>†</sup> Both subjects were = 40 years old; reasons for hysterectomy were bleeding (1) and pain/myoma (1)



## Results

### A. Primary Effectiveness Endpoint

Patient success was based on a reduction in diary score from  $\geq 150$  pre-treatment to  $\leq 75$  at one year. The results are presented below:

**Table 4a -- Effectiveness: Diary Scores at 1 year**

	<b>HTA®</b> n = 187 <sup>†</sup>	<b>RB</b> n = 89 <sup>†</sup>
number of successful subjects (diary score = 75)	128	68
study success rate (# successful/total subjects)	68.4%	76.4%
number of subjects with amenorrhea (diary score = 0)	66	42
amenorrhea rate (# with diary score = 0/total subjects)	35.3%	47.1%

<sup>†</sup> This table presents the intent-to-treat results of the study data. See "Subject Accountability" section above for accountability of all subjects enrolled in study.

### B. Secondary Effectiveness Endpoint

Results with respect to the secondary endpoint of quality of life (QoL) compared QoL scores at pre-treatment and 12-months post-treatment for both HTA® and RB study groups, and are presented in the table below:

**Table 4b -- Effectiveness: Quality of Life (QoL) at 1 year**

	<b>HTA®</b>	<b>RB</b>
number of subjects who responded to questionnaire	167	83
QoL score (mean $\pm$ SD) <sup>†</sup>		
@ baseline	54.2 $\pm$ 13.5	53.3 $\pm$ 13.5
@ 1 year	13.0 $\pm$ 15.0	11.4 $\pm$ 15.2
leisure activities affected		
@ baseline	70.1%	66.3%
@ 1 year	21.6%	28.9%
work and activities of daily life affected		
@ baseline	90.4%	91.0%
@ 1 year	19.8%	20.0%

<sup>†</sup> The QoL information was obtained from the Ruta QoL questionnaire (*Ruta DA, Garratt AM, Chadha YC, et al. Assessment of patients with menorrhagia: how valid is a structured clinical history as a measure of health status? Qual Life Res 4:33-40, 1995.*). The scoring scale range was 2.6 - 89.5. A higher score is associated with increased menorrhagia (e.g., mild = 37.6; moderate = 46.7; and severe = 50.7).

### C. Safety Endpoints

Results related to safety information were provided in terms of adverse event information, overall time of treatment, and type of anesthesia provided. Adverse event information is described in the "Adverse Events" section above. Overall treatment time was  $26.4 \pm 12.1$  minutes for HTA® and  $32.2 \pm 12.2$  minutes for RB.

Anesthesia was delivered at the discretion of the investigator and attending anesthesiologist. General anesthesia was administered to 55% and 76% of HTA® and RB subjects, respectively. Thirty percent of HTA® subjects received a paracervical block with IV sedation as compared to 13% of RB subjects. Fifteen percent of HTA® subjects received paracervical block without IV sedation, as compared to 9% of RB subjects.

## **XI. CONCLUSIONS DRAWN FROM THE STUDIES**

The pre-clinical and clinical studies provide reasonable assurance that the HTA® is safe and effective, when used in accordance with the directions for use in the ablation of the endometrial lining of the uterus in premenopausal women with menorrhagia due to benign causes for whom childbearing is complete.

## **XII. PANEL RECOMMENDATION**

In accordance with the provisions of section 515(c)(2) of the Federal Food, Drug and Cosmetic Act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Obstetrics and Gynecology Devices Advisory Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

## **XIII. FDA DECISION**

FDA issued an approval order on April 20, 2001.

The applicant's manufacturing facilities were inspected on October 16, 23, and 24, 2000 and found to be in compliance with Quality Systems Regulation.

## **XIV. 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.

Post-approval Requirements and Restrictions: The applicant is required to follow subjects from the Phase III (pivotal safety and effectiveness) study for a period of three years from the time of treatment in order to collect long-term safety and effectiveness data on the HTA®. In addition, the device is restricted to physicians trained in diagnostic hysteroscopy.